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(54) **Novel 7-(substituted)-8-(substituted)-9-(substituted glycyl)amido-6-demethyl-6-deoxytetracyclines**

7-(subtituierte)-8-(substituierte)-9-(substituiertes Glycyl)amido-6-demethyl-6-deoxytetracycline

(Substituées)-7 (substituées)-9 (substitué glycyl)amido-6 déméthyl-6 déoxy-6 tétracyclines

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(56) References cited:
EP-A- 0 536 515 **US-A- 3 338 963**

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Description

1. Field of the Invention

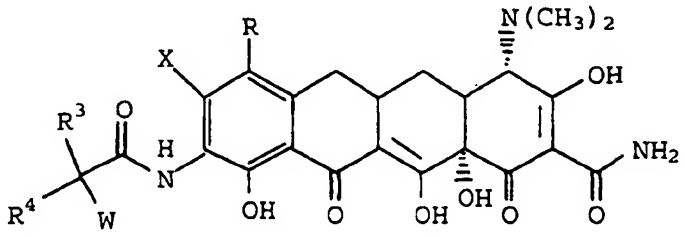
[0001] The invention relates to novel [4S-(4aalpha,12aalpha)]-4-(dimethylamino)-7-(substituted)-8-(substituted) -9-[[(substituted amino)substituted]amino]1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamides, herein after called 7-(substituted)-8-(substituted)-9-[(substituted glycyl)amido]-6-demethyl-6-deoxytetracyclines, which exhibit antibiotic activity against a wide spectrum of organisms including organisms which are resistant to tetracyclines and are useful as antibiotic agents.

[0002] The invention also relates to novel 9-[(haloacyl)amido]-7-(substituted)-8-(substituted)-6-demethyl-6-deoxytetracycline intermediates useful for making the novel compounds of the present invention and to novel methods for producing the novel compounds and intermediate compounds.

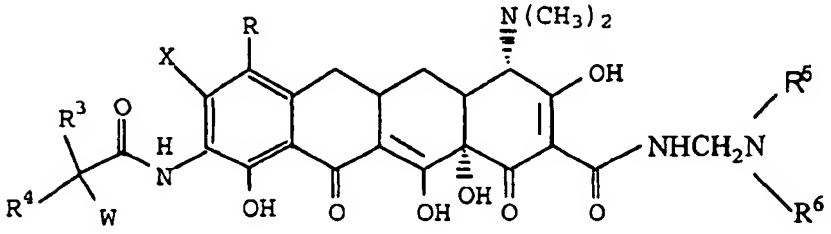
SUMMARY OF THE INVENTION

[0003] This invention is concerned with novel 7-(substituted)-8-(substituted)-9-[(substituted glycyl)-amido]-6-demethyl-6-deoxytetracyclines, represented by formula I and II, which have antibacterial activity; with methods of treating infectious diseases in warm blooded animals employing these compounds; with pharmaceutical preparations containing these compounds; with novel intermediate compounds and processes for the production of these compounds. More particularly, this invention is concerned with compounds of formula I and II which have enhanced antibiotic activity against tetracycline resistant strains as well as a high level of activity against strains which are normally susceptible to tetracyclines.

[0004] Provided by the invention are compounds of the formula:



I



II

[0005] In formula I and II,

X is halogen or trifluoromethanesulfonyloxy, the halogen is selected from bromine, chlorine, fluorine and iodine; R is selected from hydrogen; halogen selected from bromine, chlorine, fluorine and iodine; or R = $-NR^1R^2$ and when R = $-NR^1R^2$ and R^1 = hydrogen,

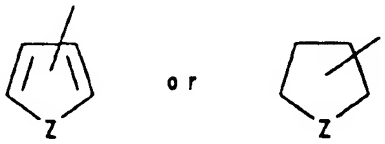
R^2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl;
and when R^1 = methyl or ethyl,
R^2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;
and when R^1 = n-propyl,
R^2 = n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;
and when R^1 = 1-methylethyl,
R^2 = n-butyl, 1-methylpropyl or 2-methylpropyl;
and when R^1 = n-butyl,
R^2 = n-butyl, 1-methylpropyl or 2-methylpropyl;
and when R^1 = 1-methylpropyl, R^2 = 2-methylpropyl;
R^3 is selected from hydrogen; straight or branched (C_1-C_8)alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and octyl; α-mercapto(C_1-C_4)alkyl group selected from mercaptomethyl, α-mercaptoethyl, α-mercapto-1-methylethyl, α-mercaptopropyl and α-mercaptobutyl;
α-hydroxy(C_1-C_4)alkyl group selected from hydroxymethyl, α-hydroxyethyl, α-hydroxy-1-methylethyl, α-hydroxypropyl and α-hydroxybutyl; carboxyl(C_1-C_8)-alkyl group; (C_6-C_{10})aryl group selected from phenyl, α-naphthyl and β-naphthyl; substituted(C_6-C_{10})aryl group (substitution selected from hydroxy, halogen, (C_1-C_4)alkoxy, trihalo(C_1-C_3)alkyl, nitro, amino, cyano, (C_1-C_4)alkoxycarbonyl, (C_1-C_3)alkylamino and carboxy); (C_7-C_9)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenylpropyl; substituted(C_7-C_9)aralkyl group [substitution selected from halo, (C_1-C_4)alkyl, nitro, hydroxy, amino, mono- or disubstituted (C_1-C_4)alkylamino, (C_1-C_4)alkoxy, (C_1-C_4)alkylsulfonyl, cyano and carboxy];
R^4 is selected from hydrogen and (C_1-C_6)alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl;
when R^3 does not equal R^4 the stereochemistry of the asymmetric carbon (i.e., the carbon bearing the W substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D);
W is selected from amino; hydroxylamino; (C_1-C_{12}) straight or branched alkyl monosubstituted amino group substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1-methyl-1-ethylpropyl, heptyl, octyl, nonyl, decyl, undecyl and dodecyl and the diastereomers and enantiomers of said branched alkyl monosubstituted amino group;
(C_3-C_8)cycloalkyl monosubstituted amino group substitution selected from cyclopropyl, trans-1,2-dimethylcyclopropyl, cis-1,2-dimethylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]-hept-2-yl, and bicyclo[2.2.2]oct-2-yl and the diastereomers and enantiomers of said (C_3-C_8)cycloalkyl monosubstituted amino; [(C_4-C_{10})cycloalkyl]alkyl monosubstituted amino group substitution selected from (cyclopropyl)methyl, (cyclopropyl)ethyl, (cyclobutyl)-methyl, (trans-2-methylcyclopropyl)methyl, and (cis-2-methylcyclobutyl)methyl; (C_3-C_{10})alkenyl monosubstituted amino group substitution selected from allyl, 3-butenyl, 2-butenyl(cis or trans), 2-pentenyl, 4-octenyl, 2,3-dimethyl-2-butenyl, 3-methyl-2-butenyl, 2-cyclopentenyl and 2-cyclohexenyl; (C_6-C_{10})aryl monosubstituted amino group substitution selected from phenyl and naphthyl; (C_7-C_{10})aralkylamino group substitution selected from benzyl, 2-phenylethyl, 1-phenylethyl, 2-(naphthyl)methyl, 1-(naphthyl)methyl and phenylpropyl; substituted (C_6-C_{10})aryl monosubstituted amino group [substitution selected from (C_1-C_5)acyl, (C_1-C_5) acylamino, (C_1-C_4)alkyl, mono or disubstituted (C_1-C_8)alkylamino, (C_1-C_4)alkoxy, (C_1-C_4)alkoxycarbonyl, (C_1-C_4) alkylsulfonyl, amino, carboxy, cyano, halogen, hydroxy, nitro and trihalo(C_1-C_3)alkyl]; straight or branched symmetrical disubstituted (C_2-C_{14})alkylamino group substitution selected from dimethyl, diethyl, diisopropyl, di-n-propyl, dibutyl and diisobutyl; symmetrical disubstituted (C_3-C_{14})cycloalkylamino group substitution selected from dicyclopropyl, dicyclobutyl, dicyclopentyl, dicyclohexyl and dicycloheptyl; straight or branched unsymmetrical disubstituted (C_3-C_{14})alkylamino group wherein the total number of carbons in the substitution is not more than 14; unsymmetrical disubstituted (C_4-C_{14})cycloalkylamino group wherein the total number of carbons in the substitution is not more than 14; (C_2-C_8)azacycloalkyl and substituted (C_2-C_8)-azacycloalkyl group substitution selected from aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, 4-methylpiperidinyl, 2-methylpyrrolidinyl, cis-3,4-dimethylpyrrolidinyl, trans-3,4-dimethylpyrrolidinyl, 2-azabicyclo[2.1.1]hex-2-yl, 5-azabicyclo[2.1.1]hex-5-yl, 2-azabicyclo[2.2.1]-hept-2-yl, 7-azabicyclo[2.2.1]hept-7-yl, 2-azabicyclo-[2.2.2]oct-2-yl and the diastereomers and enantiomers of said (C_2-C_8)azacycloalkyl and substituted (C_2-C_8)-azacycloalkyl group; 1-azaoxacycloalkyl selected from morpholinyl and 1-aza-5-oxocycloheptane; substituted 1-azaoxacycloalkyl group substitution selected from 2-(C_1-C_3)alkylmorpholinyl, 3-(C_1-C_3)alkylisoxazolidinyl, tetrahydrooxazinyl and 3,4-dihydrooxazinyl; [1,n]-diazacycloalkyl and substituted [1,n]-diazacycloalkyl group selected from piperazinyl, 2-(C_1-C_3)alkylpiperazinyl, 4-(C_1-C_3)alkylpiperazinyl, 2,4-dimethylpiperazinyl, 4-(C_1-C_4)alkoxypiperazinyl, 4- (C_6-C_{10}) -aryloxypiperazinyl, 4-hydroxypiperazinyl, 2,5-diazabicyclo-[2.2.1]-hept-2-yl, 2,5-diaza-5-methylbicyclo-[2.2.1]hept-2-yl, 2,3-diaza-3-methylbicyclo-[2.2.2]oct-2-yl, 2,5-diaza-5,7-dimethylbicyclo-[2.2.2]oct-2-yl and the diastereomers or enantiomers of said [1,n]-diazacycloalkyl

and substituted [1,n]-diazacycloalkyl group; 1-azathiacycloalkyl and substituted 1-azathiacycloalkyl group selected from thiomorpholinyl, 2-(C_1-C_3)alkylthio-morpholinyl and 3-(C_3-C_6)cycloalkylthiomorpholinyl; N-azolyl and substituted N-azolyl group selected from 1-imidazolyl, 2-(C_1-C_3)alkyl-1-imidazolyl, 3-(C_1-C_3)alkyl-1-imidazo-lyl, 1-pyrrolyl, 1-pyrazolyl, 2-(C_1-C_3)alkyl-1-pyrrolyl, 3-(C_1-C_3)-alkyl-1-pyrazolyl, Indolyl, 1-(1,2,3-triazolyl), 4-(C_1-C_3)alkyl-1-(1,2,3-triazolyl), 5-(C_1-C_3)alkyl-1-(1,2,3-triazolyl), 4-(1,2,4-triazolyl, 1-tetrazolyl, 2-tetrazolyl and benzimidazolyl; (heterocycle)amino group selected from 2- or 3-furanylamino, 2- or 3-thienylamino, 2-, 3- or 4-pyridylamino, 2- or 5-pyridazinylamino, 2-pyrazinylamino, 2-(imidazolyl)amino, (benzimidazolyl)amino, and (benzothiazolyl)amino) amino and substituted(heterocycle)amino group as defined above with substitution selected from straight or branched (C_1-C_6) alkyl; (heterocycle)methyl-amino group selected from 2- or 3-furylmethylamino, 2- or 3-thienylmethylamino, 2-, 3- or 4-pyridylmethylamino, 2- or 5-pyridazinylmethylamino, 2-pyrazinylmethyl-amino, 2-(imidazolyl)methylamino, (benzimidazolyl)methylamino, and (benzothiazolyl)methylamino and substituted (heterocycle) methylamino group as defined above with substitution selected from straight or branched (C_1-C_6)alkyl; carboxy (C_2-C_4)alkylamino group selected from aminoacetic acid, α-aminopropionic acid, β-aminopropionic acid, α-butyric acid, and β-aminobutyric acid and the enantiomers of said carboxy(C_2-C_4)alkylamino group; (C_1-C_4)alkoxycarbonylamino group substitution selected from methoxycarbonyl, ethoxycarbonyl, allyloxycarbonyl, propoxycarbonyl, isoproproxycarbonyl, 1,1-dimethylethoxycarbonyl, n-butoxycarbonyl, and 2-methylpropoxycarbonyl; (C_1-C_4) alkoxyamino group substitution selected from methoxy, ethoxy,n-propoxy, 1-methylethoxy, n-butoxy, 2-methylpropoxy, and 1,1-dimethylethoxy;

(C_3-C_8)cycloalkoxyamino group selected from cyclopropoxy, trans-1,2-dimethylcyclopropoxy, cis-1,2-dimethylcyclopropoxy, cyclobutoxy, cyclopentoxy, cyclohexoxy, cycloheptoxy, cyclooctoxy, bicyclo[2.2.1]hept-2-yloxy, bicyclo [2.2.2]oct-2-yloxy and the diastereomers and enantiomers of said (C_3-C_8)cycloalkoxyamino group;

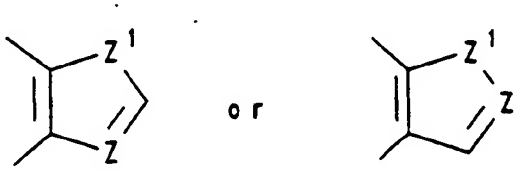
(C_6-C_{10})aryloxyamino group selected from phenoxyamino, 1-naphthyloxyamino and 2-naphthyloxyamino; (C_7-C_{11})-arylalkoxyamino group substitution selected from benzyloxy, 2-phenylethoxy, 1-phenylethoxy, 2-(naphthyl) methoxy, 1-(naphthyl)methoxy and phenylpropoxy;

R^5 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (C_6-C_{10})aryl group selected from phenyl, α-naphthyl or β-naphthyl; (C_7-C_9)aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:



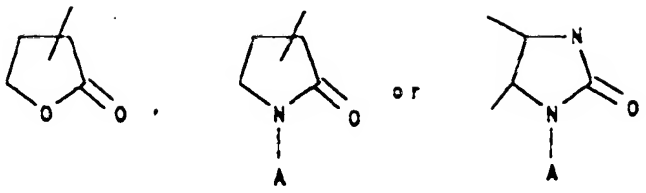
Z = N, O, S or Se

such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

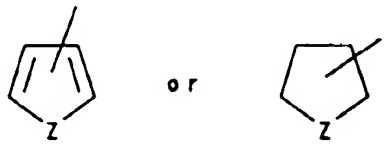


Z or Z^1 = N, O, S or Se

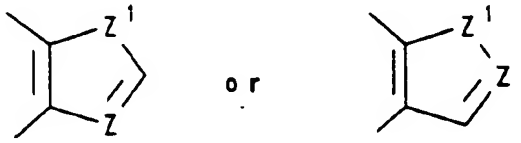
such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-imidazo[4,5-b]pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



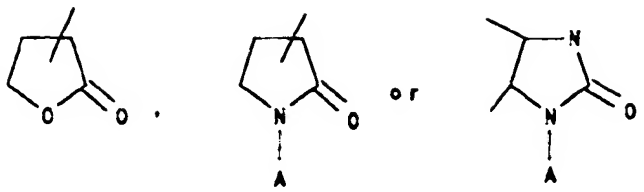
(A is selected from hydrogen; straight or branched (C_1-C_4)alkyl: C_6-aryl; substituted C_6-aryl (substitution selected from halo,(C_1-C_4)alkoxy, trihalo(C_1-C_3)-alkyl, nitro, amino, cyano, (C_1-C_4)alkoxycarbonyl, (C_1-C_3)alkylamino or carboxy); (C_7-C_9)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)
such as γ-butyrolactam, γ-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, sym-triazinyl, unsym-triazinyl, pyrimidinyl or (C_1-C_3)alkylthiopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxo-1-piperazinyl, 2-dioxomorpholinyl, 2-dioxothiomorpholinyl; or $-(CH_2)_nCOOR^7$ where n=0-4 and R^7 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl ; or (C_6-C_{10})aryl group selected from phenyl, α-naphthyl, or β-naphthyl;
R^6 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (C_6-C_{10})aryl group selected from phenyl, α-naphthyl or β-naphthyl; (C_7-C_9)aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:



Z – N, O, S or Se
such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:



Z or Z^1 – N, O, S or Se
such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-imidazo[4,5-b]pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



(A is selected from hydrogen; straight or branched (C_1-C_4)alkyl; C_6-aryl; substituted C_6-aryl (substitution selected from halo,(C_1-C_4)alkoxy, trihalo(C_1-C_3)-alkyl, nitro, amino, cyano, (C_1-C_4)alkoxycarbonyl, (C_1-C_3)alkylamino or carboxy); (C_7-C_9)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)
such as γ-butyrolactam, γ-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, sym-triazinyl, unsymtriazinyl, pyrimidinyl or (C_1-C_3)alkylthiopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxo-1-piperazinyl, 2-dioxomorpholinyl, 2-dioxothiomorpholinyl; or -(CH_2)nCOOR^7 where n=0-4 and R^7 is selected from hydrogen; straight or branched (C_1-C_3)alkyl selected from methyl, ethyl, n-propyl or 1-methylethyl; or (C_6-C_{10})aryl selected from phenyl, α-naphthyl or β-naphthyl; with the proviso that R^5 and R^6 cannot both be hydrogen;
or R^5 and R^6 taken together are - $(CH_2)_2B(CH_2)_2$-, wherein B is selected from $(CH_2)_n$ and n=0-1, -NH, -N(C_1-C_3) alkyl [straight or branched], -N(C_1-C_4)alkoxy, oxygen, sulfur or substituted congeners selected from (L or D)proline or ethyl(L or D)prolinate; and the pharmacologically acceptable organic and inorganic salts or metal complexes.

[0006] Preferred compounds are compounds according to the above formula I and II wherein: X is halogen or trifluoromethanesulfonyloxy, the halogen is selected from bromine, chlorine, fluorine and iodine; R is selected from hydrogen; halogen selected from bromine, chlorine and iodine; or R = -NR^1R^2

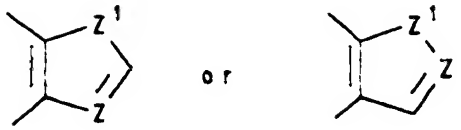
and when R = -NR^1R^2
and R^1 = hydrogen, R^2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;
and when R^1 = methyl or ethyl,
R^2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;
R^3 is selected from hydrogen; straight or branched (C_1-C_8)alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and octyl; α-hydroxy(C_1-C_4)alkyl group selected from hydroxymethyl, α-hydroxyethyl, α-hydroxy-1-methylethyl,α-hydroxypropyl and α-hydroxybutyl; carboxyl(C_1-C_8)-alkyl group; (C_6-C_{10}) aryl group selected from phenyl, α-naphthyl and β-naphthyl; substituted(C_6-C_{10})aryl group (substitution selected from hydroxy, halogen,
(C_1-C_4)alkoxy, (C_1-C_4)alkoxycarbonyl, and carboxy);
(C_7-C_9)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenylpropyl; substituted(C_7-C_9)aralkyl group [substitution selected from halo, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)alkylsulfonyl, cyano and carboxy];
R^4 is selected from hydrogen and (C_1-C_4)alkyl selected from methyl, ethyl propyl, isopropyl, butyl and isobutyl;
when R^3 does not equal R^4 the stereochemistry of the asymmetric carbon (i.e., the carbon bearing the W substituent) maybe either the racemate (DL) or the individual enantiomers (L or D);
W is selected from amino; hydroxylamino; (C_1-C_{12}) straight or branched alkyl monosubstituted amino group substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1-methyl-1-ethylpropyl, heptyl, octyl, nonyl, decyl and the diastereomers and enantiomers of said branched alkyl monosubstituted amino group; (C_3-C_8)cycloalkyl monosubstituted amino group substitution selected from cyclopropyl, trans-1,2-dimethylcyclopropyl, cis-1,2-dimethylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the diastereomers and enantiomers of said (C_3-C_8)cycloalkyl monosubstituted amino group; [(C_4-C_{10})cycloalkyl]alkyl monosubstituted amino group substitution selected from (cyclopropyl)methyl, (cyclopropyl)ethyl, (cyclobutyl)methyl, (trans-2-methylcyclopropyl)methyl and (cis-2-methylcyclobutyl)methyl; (C_3-C_{10})alkenyl monosubstituted amino group substitution selected from allyl, 3-butenyl, 2-butenyl (cis or trans), 2-pentenyl, 4-octenyl, 2 3-dimethyl-2-butenyl, 3-methyl-2-butenyl, 2-cyclopentenyl and 2-cyclohexenyl; (C_7-C_{10})aralkylamino group substitution se-

lected from benzyl, 2-phenylethyl, 1-phenylethyl, 2-(naphthyl)methyl, 1-(naphthyl)methyl and phenylpropyl; straight or branched symmetrical disubstituted (C_2-C_{14})alkylamino group substitution selected from dimethyl, diethyl, diisopropyl, di-n-propyl, dibutyl and diisobutyl; symmetrical disubstituted (C_3-C_{14})-cycloalkylamino group substitution selected from dicyclopropyl, dicyclobutyl, dicyclopentyl, dicyclohexyl and dicycloheptyl; straight or branched unsymmetrical disubstituted (C_3-C_{14})alkyl amino group wherein the total number of carbons in the substitution is not more than 14; unsymmetrical disubstituted (C_4-C_{14})cycloalkylamino group wherein the total number of carbons in the substitution is not more than 14;

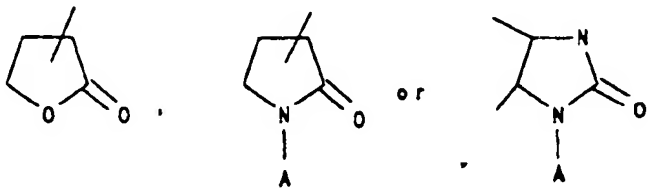
(C_2-C_8)azacycloalkyl and substituted (C_2-C_8)azacycloalkyl group substitution selected from aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, 4-methylpiperidinyl, 2-methylpyrrolidinyl, cis-3,4-dimethylpyrrolidinyl, trans-3,4-dimethylpyrrolidinyl, 2-azabicyclo[2.1.1]hex-2-yl, 5-azabicyclo-[2.1.1]hex-5-yl, 2-azabicyclo[2.2.1]hept-2-yl, 7-azabicyclo [2.2.1]hept-7-yl, 2-azabicyclo[2.2.2]oct-2-yl and the diastereomers and enantiomers of said (C_2-C_8)azacycloalkyl and substituted (C_2-C_8)azacycloalkyl group; 1-azaoxacycloalkyl selected from morpholinyl and 1-aza-5-oxocycloheptane; substituted 1-azaoxacycloalkyl group substitution selected from 2-(C_1-C_3)alkylmorpholinyl, 3-(C_1-C_3) alkylisoxazolidinyl, tetrahydrooxazinyl and 3,4-dihydrooxazinyl; [1,n]-diazacycloalkyl and substituted [1,n]-diazacycloalkyl group selected from piperazinyl, 2-(C_1-C_3)alkylpiperazinyl, 4-(C_1-C_3)alkylpiperazinyl, 2,4-dimethylpiperazinyl, 4-(C_1-C_4)alkoxypiperazinyl, 2,5-diazabicyclo[2.2.1]hept-2-yl, 2,5-diaza-5-methylbicyclo[2.2.1]hept-2-yl, 2,3-diaza-3-methylbicyclo[2.2.2]-oct-2-yl, and the diastereomers or enantiomers of said [1,n]-diazacycloalkyl and substituted [1,n]-diazacycloalkyl group; 1-azathiacycloalkyl and substituted 1-azathiacycloalkyl group selected from thiomorpholinyl, 2-(C_1-C_3)alkylthiomorpholinyl and 3-(C_3-C_6)cycloalkylthiomorpholinyl; N-azolyl and substituted N-azolyl group selected from 1-imidazolyl, 2-(C_1-C_3)alkyl-1-imidazolyl, 3-(C_1-C_3)alkyl-1-imidazolyl, 1-pyrrolyl, 2-(C_1-C_3)alkyl-l-pyrrolyl, 3-(C_1-C_3)alkyl-1-pyrazolyl, indolyl, 1-(1,2,3-triazolyl), 4-(C_1-C_3)alkyl-1-(1,2,3-triazolyl), 5-(C_1-C_3)alkyl-1-(1,2,3-triazolyl) and 4-(1,2,4-triazolyl); (heterocycle)methylamino group said heterocycle selected from 2- or 3-furylmethylamino, 2- or 3-thienylmethylamino, 2-, 3-or 4-pyridylmethylamino, 2- or 5-pyridazinylmethylamino, 2-pyrazinylmethylamino, 2-(imidazolyl)-methylamino, (benzimidazolyl)methylamino, and (benzothiazolyl)methylamino and substituted (heterocycle)amino group as defined above with substitution selected from straight or branched (C_1-C_6)alkyl; carboxy(C_2-C_4)alkylamino group selected from aminoacetic acid, α-aminopropionic acid, β-aminopropionic acid, α-butyric acid, β-aminobutyric acid and the enantiomers of said carboxy (C_2-C_4)alkylamino group; (C_1-C_4)alkoxycarbonylamino group substitution selected from methoxycarbonyl, ethoxycarbonyl, allyloxycarbonyl, propoxycarbonyl, isoproproxycarbonyl, 1,1-dimethylethoxycarbonyl, n-butoxycarbonyl, and 2-methylpropoxycarbonyl; (C_1-C_4)alkoxyamino group substitution selected from methoxy, ethoxy, n-propoxy, 1-methylethoxy, n-butoxy, 2-methylpropoxy, and 1,1-dimethylethoxy; (C_3-C_8)cycloalkoxyamino group selected from cyclopropoxy, trans-1,2-dimethylcyclopropoxy, cis-1,2-dimethylcyclopropoxy, cyclobutoxy, cyclopentoxy, cyclohexoxy, cycloheptoxy, cyclooctoxy, bicyclo[2.2.1]hept-2-yloxy, bicyclo[2.2.2]oct-2-yloxy and the diastereomers and enantiomers of said (C_3-C_8)cycloalkoxyamino group; (C_7-C_{11})arylalkoxyamino group substitution selected from benzyloxy, 2-phenylethoxy, 1-phenylethoxy, 2-(naphthyl)methoxy, 1-(naphthyl)methoxy and phenylpropoxy; R^5 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (C_6-C_{10})aryl group selected from phenyl, α-naphthyl or β-naphthyl; (C_7-C_9)aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

Z – N, O, S or Se

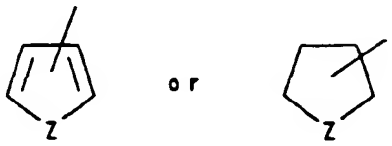
such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:



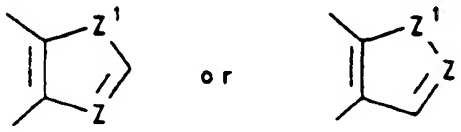
Z or Z^1 = N, O, S or Se
such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-imidazo[4,5-b]pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



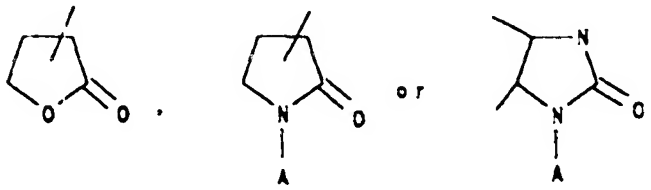
(A is selected from hydrogen; straight or branched (C_1-C_4)alkyl; C_6-aryl; (C_7-C_9)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)
such as γ-butyrolactam, γ-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, sym-triazinyl, unsymtriazinyl, pyrimidinyl or (C_1-C_3)alkylthiopyridazinyl;
or - $(CH_2)_nCOOR^7$ where n=0-4 and R^7 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl;
or (C_6-C_{10})aryl group selected from phenyl, α-naphthyl, or β-naphthyl;
R^6 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (C_6-C_{10})aryl group selected from phenyl, α-naphthyl or β-naphthyl; (C_7-C_9)aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:



Z – N, O, S or Se
such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:



Z or Z^1 – N, O, S or Se
such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-imidazo[4,5-b]pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

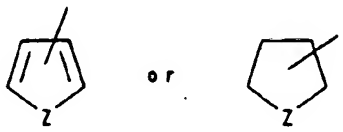


(A is selected from hydrogen; straight or branched (C_1-C_4)alkyl; C_6-aryl; (C_7-C_9)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)
such as γ-butyrolactam, γ-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, sym-triazinyl, unsymtriazinyl, pyrimidinyl or (C_1-C_3)alkylthiopyridazinyl;
or -$(CH_2)_n$COOR^7 where n=0-4 and R^7 is selected from hydrogen; straight or branched (C_1-C_3)alkyl selected from methyl, ethyl, n-propyl or 1-methylethyl; or
(C_6-C_{10})aryl selected from phenyl, α-naphthyl or β-naphthyl; with the proviso that R^5 and R^6 cannot both be hydrogen; or R^5 and R^6 taken together are -$(CH_2)_2B(CH_2)_2$-, wherein B is selected from $(CH_2)_n$ and n=0-1, -NH, -N(C_1-C_3) alkyl [straight or branched], -N(C_1-C_4)alkoxy, oxygen, sulfur or substituted congeners selected from (L or D)proline or ethyl(L or D)prolinate; and the pharmacologically acceptable organic and inorganic salts or metal complexes.

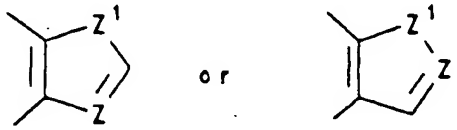
[0007] Particularly preferred compounds are compounds according to the above formula I and II wherein:

X is halogen or trifluoromethanesulfonyloxy, the halogen is selected from bromine, chlorine, fluorine and iodine;
R is selected from hydrogen; halogen selected from bromine, chlorine and iodine;
or R – -NR^{1}R^2
and when R – -NR^{1}R^2 and R^1 – hydrogen,
R^2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl;
and when R1 – methyl or ethyl,
R^2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;
R^3 is selected from hydrogen; straight or branched (C_1-C_6)alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl;
(C_6-C_{10})aryl group selected from phenyl, α-naphthyl and β-naphthyl; (C_7-C_9)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenylpropyl;
R^4 is selected from hydrogen and (C_1-C_4)alkyl selected from methyl, ethyl propyl, isopropyl, butyl and isobutyl;
when R^3 does not equal R^4 the stereochemistry of the asymmetric carbon (i.e., the carbon bearing the W substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D);
W is selected from amino; (C_1-C_{12}) straight or branched alkyl monosubstituted amino group substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 3-methylbutyl,n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1-methyl-1-ethylpropyl and the diastereomers and enantiomers of said branched alkyl monosubstituted amino group; (C_3-C_5)cycloalkyl monosubstituted amino group substitution selected from cyclopropyl, trans-1,2-dimethylcyclopropyl, cis-1,2-dimethylcyclopropyl, cyclobutyl and the diastereomers and enantiomers of said (C_3-C_5)cycloalkyl monosubstituted amino group; [(C_4-C_{10})cycloalkyl]alkyl monosubstituted amino group substitution selected from (cyclopropyl)methyl, (cyclopropyl) ethyl and (cyclobutyl)methyl; (C_3-C_{10})-alkenyl monosubstituted amino group substitution selected from allyl, 3-butenyl 2-butenyl (cis or trans), 2-pentenyl, 4-octenyl, 2,3-dimethyl-2-butenyl, 3-methyl-2-butenyl, 2-cyclopentenyl and 2-cyclohexenyl; (C_7-C_{10})aralkylamino group substitution selected from benzyl, 2-phenylethyl, 1-phenylethyl, 2-(naphthyl)-methyl, 1-(naphthyl)methyl and phenylpropyl; straight or branched symmetrical disubstituted (C_2-C_{14})alkylamino group substitution selected from dimethyl, diethyl, diisopropyl, and di-n-propyl; straight or branched

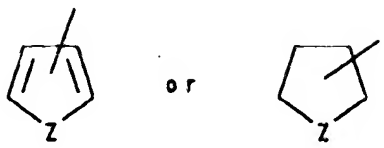
unsymmetrical disubstituted (C_2-C_{14})alkylamine group wherein the total number of carbons in the substitution is no more than 14; unsymmetrical disubstituted (C_4-C_{14})cycloalkylamino group wherein the total number of carbons in the substitution is no more than 14; (C_2-C_8)azacycloalkyl and substituted (C_2-C_8)-azacycloalkyl group substitution selected from aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, 4-methylpiperidinyl, 2-methylpyrrolidinyl, cis-3,4-dimethylpyrrolidinyl, trans-3,4-dimethylpyrrolidinyl and the diastereomers and enantiomers of said (C_2-C_8)azacycloalkyl and substituted (C_2-C_8)-azacycloalkyl group; 1-azaoxacycloalkyl selected from morpholinyl and 1-aza-5-oxocycloheptane; substituted 1-azaoxacycloalkyl group substitution selected from 2-(C_1-C_3)alkylmorpholinyl, 3-(C_1-C_3)alkylisoxazolidinyl and tetrahydrooxazinyl; [1,n]-diazacycloalkyl and substituted [1,n]-diazacycloalkyl group selected from piperazinyl, 2-(C_1-C_3)alkylpiperazinyl, 4-(C_1-C_3)alkylpiperazinyl, 2,4-dimethylpiperazinyl, 2,5-diazabicyclo-[2.2.1]hept-2-yl, 2,5-diaza-5-methylbicyclo[2.2.1]-hept-2-yl, 2,3-diaza-3-methylbicyclo[2.2.2]oct-2-yl, and the diastereomers or enantiomers of said [1,n]-diazacycloalkyl and substituted [1,n]-diazacycloalkyl group; 1-azathiacycloalkyl and substituted 1-azathiacycloalkyl group selected from thiomorpholinyl and 2-(C_1-C_3)alkylthiomorpholinyl; N-azolyl and substituted N-azolyl group selected from 1-imidazolyl, indolyl, 1-(1,2,3-triazolyl) and 4-(1,2,4-triazolyl); (heterocycle)methylamino group selected from 2- or 3-furylmethylamino, 2- or 3-thienylmethylamino and 2-, 3- or 4-pyridylmethylamino; (C_1-C_4)alkoxycarbonylamino group substitution selected from methoxycarbonyl, ethoxycarbonyl, allyloxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, 1,1-dimethylethoxycarbonyl, n-butoxycarbonyl, and 2-methylpropoxycarbonyl; (C_1-C_4)alkoxyamino group substitution selected from methoxy, ethoxy, n-propoxy, 1-methylethoxy, n-butoxy, 2-methylpropoxy, and 1,1-dimethylethoxy;
(C_7-C_{11})arylalkoxyamino group substitution selected from benzyloxy, 2-phenylethoxy, 1-phenylethoxy, 2-(naphthyl)methoxy, 1-(naphthyl)methoxy and phenylpropoxy ;
R^5 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (C_6-C_{10})aryl group selected from phenyl, α-naphthyl or β-naphthyl; (C_7-C_9)aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:



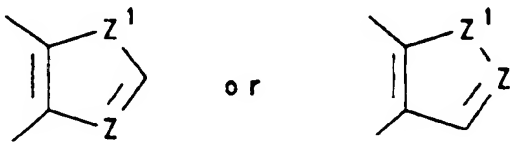
Z – N, O, S or Se
such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:



Z or Z^1 = N, O, S or Se
such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl,3-alkyl-3H-imidazo[4,5-b]pyridyl or pyridylimidazolyl; or - $(CH_2)_nCOOR^7$ where n=0-4 and R^7 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl;
or (C_6-C_{10})aryl group selected from phenyl, α-naphthyl, or β-naphthyl;
R^6 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (C_6-C_{10})aryl group selected from phenyl, α-naphthyl or β-naphthyl; (C_7-C_9)aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:



Z = N, O, S or Se
such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

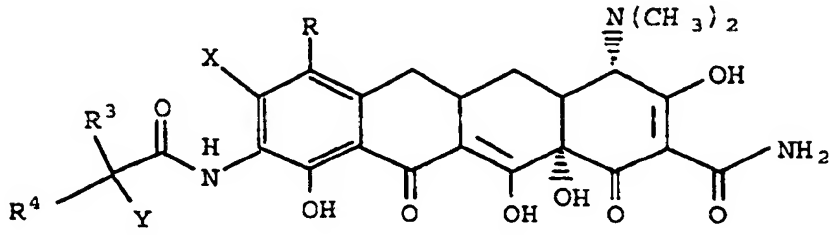


Z or Z^1 = N, O, S or Se
such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-imidazo[4,5-b]pyridyl or pyridylimidazolyl; or $-(CH_2)_nCOOR^7$ where n=0-4 and R^7 is selected from hydrogen; straight or branched (C_1-C_3)-alkyl selected from methyl, ethyl, n-propyl or 1-methylethyl; or (C_6-C_{10})aryl selected from phenyl, α-naphthyl or β-naphthyl; with the proviso that R^5 and R^6 cannot both be hydrogen; or R^5 and R^6 taken together are - $(CH_2)_2B(CH_2)_2$-, wherein B is selected from $(CH_2)_n$ and n=0-1, -NH, $-N(C_1-C_3)$alkyl [straight or branched], $-N(C_1-C_4)$alkoxy, oxygen, sulfur or substituted congeners selected from (L or D)proline or ethyl(L or D)prolinate; and the pharmacologically acceptable organic and inorganic salts or metal complexes.

[0008] Compounds of special interest are compounds according to the above formula I and II wherein: X is halogen or trifluoromethanesulfonyloxy, the halogen is selected from chlorine and fluorine; R is selected from hydrogen; halogen selected from chlorine and iodine; or

R = $-NR^1R^2$
and when R = $-NR^1R^2$ and R^1 = methyl or ethyl,
R^2 = methyl and ethyl;
R^3 is selected from hydrogen; straight or branched (C_1-C_2)alkyl group selected from methyl and ethyl;
R^4 is selected from hydrogen and (C_1-C_6)alkyl selected from methyl and ethyl;
when R^3 does not equal R^4 the stereochemistry of the asymmetric carbon (i.e., the carbon bearing the W substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D);
W is selected from amino; (C_1-C_4)straight or branched alkyl monosubstituted amino group substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl and 1-methylpropyl; (C_3-C_4)cycloalkyl monosubstituted amino group substitution selected from cyclopropyl and cyclobutyl; (C_2-C_8)azacycloalkyl and substituted (C_2-C_8)azacycloalkyl selected from pyrrolidinyl, piperidinyl and 4-methylpiperidinyl; 1-azaoxacycloalkyl selected from morpholinyl; [1,n]-diazacycloalkyl and substituted [1,n]- diazacycloalkyl group selected from piperazinyl and 4-(C_1-C_3)alkyl-piperazinyl; N-azolyl and substituted N-azolyl group selected from 1-imidazolyl, 2-(C_1-C_3)alkyl-1-imidazolyl and 3-(C_1-C_3)alkyl-1-imidazolyl; (heterocycle)methylamino group said heterocycle selected from 2-, 3- or 4-pyridylmethylamino; carboxy(C_2-C_4)alkylamino group selected from aminoacetic acid, α-aminopropionic acid, β-aminopropionic acid, α-butyric acid, β-aminobutyric acid and the enantiomers of said carboxy(C_2-C_4)-alkylamino group;
R^5 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl;
R^6 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; with the proviso that R^5 and R^6 cannot both be hydrogen; or R^5 and R^6 taken together are $-(CH_2)_2B(CH_2)_2$-, wherein B is selected from $(CH_2)_n$ and n=0-1, -NH, $-N(C_1-C_3)$alkyl [straight or branched], $-N(C_1-C_4)$alkoxy, oxygen, sulfur or substituted congeners selected from (L or D)proline, ethyl(L or D)prolinate; and the pharmacologically acceptable organic and inorganic salts or metal complexes.

[0009] Also included in the present invention are compounds useful as intermediates for producing the above compounds of formula I and II. Such inter-mediates include those having the formula III:



III

wherein:

Y is selected bromine, chlorine, fluorine and iodine; X is halogen or trifluoromethanesulfonyl, the halogen is selected from bromine, chlorine, fluorine and iodine. R is selected from hydrogen; halogen selected from bromine, chlorine, fluorine and iodine; or R = $-NR^1R^2$
and when R = $-NR^1R^2$ and R^1 = hydrogen,
R^2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl;
and when R^1 = methyl or ethyl,
R^2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;
and when R^1 = n-propyl,
R^2 = n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;
and when R^1 = 1-methylethyl,
R^2 = n-butyl, 1-methylpropyl or 2-methylpropyl;
and when R^1 = n-butyl,
R^2 = n-butyl, 1-methylpropyl or 2-methylpropyl;
and when R^1 = 1-methylpropyl,
R^2 = 2-methylpropyl;
R^3 is selected from hydrogen; straight or branched (C_1-C_8)alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and octyl; α-mercapto(C_1-C_4)alkyl group selected from mercaptomethyl, α-mercaptoethyl, α-mercapto-1-methylethyl, α-mercaptopropyl and α-mercaptobutyl; α-hydroxy-(C_1-C_4)alkyl group selected from hydroxymethyl, α-hydroxyethyl, α-hydroxy-1-methylethyl, α-hydroxy-propyl and α-hydroxybutyl; carboxyl (C_1-C_8) alkyl group; (C_6-C_{10})aryl group selected from phenyl, α-naphthyl and β-naphthyl;
substituted(C_6-C_{10})aryl group (substitution selected from hydroxy, halogen, (C_1-C_4)alkoxy, trihalo-(C_1-C_3)alkyl, nitro, amino, cyano, (C_1-C_4)alkoxy-carbonyl, (C_1-C_3)alkylamino and carboxy); (C_7-C_9)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenylpropyl; substituted (C_7-C_9) -aralkyl group [substitution selected from halo, (C_1-C_4)alkyl, nitro, hydroxy, amino, mono- or disubstituted (C_1-C_4)alkylamino, (C_1-C_4)alkoxy, (C_1-C_4) alkylsulfonyl, cyano and carboxy];
R^4 is selected from hydrogen and (C_1-C_6)alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl;
when R^3 does not equal R^4 the stereochemistry of the asymmetric carbon (i.e., the carbon bearing the W substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D): and the pharmacologically acceptible organic and inorganic salts or metal complexes.

[0010] Preferred compounds are compounds according to the above formula III wherein:

Y is selected from bromine, chlorine, flourine and iodine;
X is halogen or trifluoromethanesulfonyloxy, the halogen is selected from bromine, chlorine, fluorine and iodine;
R is selected from hydrogen; halogen selected from bromine, chlorine and iodine; or R = $-NR^1R^2$
and when R = $-NR^1R^2$ and R^1 = hydrogen,
R^2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;
and when R^1 = methyl or ethyl,

R^2 – methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;
R^3 is selected from hydrogen; straight or branched (C_1-C_6)alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and octyl; α-hydroxy(C_1-C_4)alkyl group selected from hydroxymethyl, α-hydroxyethyl, α-hydroxy-1-methylethyl, α-hydroxypropyl and α-hydroxybutyl; carboxyl (C_1-C_2)-alkyl group; (C_6-C_{10}) aryl group selected from phenyl, α-naphthyl and β-naphthyl; substituted(C_6-C_{10})aryl group (substitution selected from hydroxy, halogen, (C_1-C_4)alkoxy, (C_1-C_4)alkoxycarbonyl, and carboxy); (C_7-C_9)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenylpropyl; substituted-(C_7-C_9)aralkyl group [substitution selected from halo, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)alkylsulfonyl, cyano and carboxy];
R^4 is selected from hydrogen and (C_1-C_4)alkyl selected from methyl, ethyl propyl, isopropyl, butyl and isobutyl; when R^3 does not equal R^4 the stereochemistry of the asymmetric carbon (i.e., the carbon bearing the W substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D); and the pharmacologically acceptable organic and inorganic salts or metal complexes.

[0011] Particularly preferred compounds are compounds according to the above formula III wherein:

Y is selected from bromine, chlorine, fluorine and iodine;
X is halogen or trifluoromethanesulfonyloxy, the halogen is selected from bromine, chlorine, fluorine and iodine;
R is selected from hydrogen; halogen selected from bromine, chlorine and iodine; or R – $-NR^1R^2$
and when R = $-NR^1R^2$ and R^1 = hydrogen,
R^2 – methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl;
and when R^1 = methyl or ethyl,
R^2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;
R^3 is selected from hydrogen; straight or branched (C_1-C_6)alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl; (C_6-C_{10})aryl group selected from phenyl, α-naphthyl and β-naphthyl; (C_7-C_9) aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenylpropyl;
R^4 is selected from hydrogen and (C_1-C_4)alkyl selected from methyl, ethyl propyl, isopropyl, butyl and isobutyl; when R^3 does not equal R^4 the stereochemistry of the asymmetric carbon (i.e., the carbon bearing the W substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D); and the pharmacologically acceptable organic and inorganic salts or metal complexes.

[0012] Compounds of special interest are compounds according to the above formula III wherein:

Y is selected from bromine, chlorine, fluorine and iodine;
X is halogen or trifluoromethanesulfonyloxy, the halogen is selected from chlorine and fluorine; R is selected from hydrogen; halogen selected from chlorine and iodine; or R – $-NR^1R^2$
and when R = $-NR^1R^2$ and R^1 = methyl or ethyl,
R^2 = methyl and ethyl;
R^3 is selected from hydrogen; straight or branched (C_1-C_2)alkyl group selected from methyl and ethyl;
R^4 is selected from hydrogen and (C_1-C_6)alkyl selected from methyl and ethyl;
when R^3 does not equal R^4 the stereochemistry of the asymmetric carbon (i.e., the carbon bearing the W substituent) may be either the racemate (DL) or the individual enantiomers (L or D); and the pharmacologically acceptable organic and inorganic salts or metal complexes.

[0013] This invention also provides the following compounds having formula I as shown above with the values as indicated

[4S-(4α,12aα)]-8-Chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a, 6,11,12a-octahydro-3,10,12,12a-tetra-hydroxy-9-[[(3-methyl cyclobutyl)amino]acetyl]amino]-1,11-dioxo-2-naphthacene carboxamide
[Compound of formula I where R=NMe_2; X=Cl; W=3-methylcyclobutylamino; R^3=H; R^4=H]

[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis-(dimethyl amino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,9,10a,11-tetra hydroxy-10,12-dioxo-2-naphthacenyl]-(3-methyl-1-pyrrolidine) acetamide
[Compound of formula I where R=NMe_2; X=Cl; W=3-methylpyrrolidin-1-yl; R^3=H; R^4=H]

[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-α-cyclobutyl tetrahydro-2H-1,2-isoxazine-2-acetamide
[Compound of formula I where R=NMe_2; X=Cl; W=tetrahydro-2H-1,2-isoxazin-2-yl; R^3=H; R^4=H;cyclobutyl]

[4S-(4α,12aα)]-8-Chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a, 6,11,12a-octahydro-3,10,12, 12a-tetrahydroxy-1, 11-dioxo-9-[[phenyl[(phenylmethyl)amino]acetyl]amino]-2-naphthacene carboxamide
[Compound of formula I where R=NMe_2; X=Cl; W=phenyl(phenylmethyl)amino; R^3=H; R^4=H]

[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis(dimethyl amino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8, 10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-α-cyclopropyl-α-methyl-1-azetidine acetamide
[Compound of formula I where R=NMe_2; X=Cl; W=azetidin-1-yl; R^4=CH_3; R^3=cyclopropyl]

[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis-(dimethyl amino)-5,5a,6,6a,7,10,10a,12-octahydro-α-(1,1 dimethylethyl)-(3-methyl-4-morpholine)acetamide
[Compound of formula I where R=NMe2; X=Cl; W=3-methyl-morpholin-4-yl; R^3=TBu; R^4=H]

[4S-(4α,12aα)]-8-Chloro-9-[[(2,4-difluorophenyl)[(2-phenyl ethyl)amino]acetyl]amino]-4,7-bis(dimethyl-amino)-1, 4,4a,5,5a, 6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
[Compound of formula I where R=NMe_2; X=Cl; W=(2,4-difluoro phenyl)(2-phenylethyl)amino; R^3=H; R^4=H]

[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis(dimethyl amino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8, 10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-α-(methoxyamino)-α-methyl-2-furan acetamide
[Compound of formula I where R=NMe_2; X=Cl; W=NHOMe; R^3=furan-2-yl; R^4=CH_3]

[7S-(7α,10aα)]-4-[[9-(Aminocarbonyl)-3-chloro-4,7- bis (dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8, 10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-amino-3-[(1,1-dimethylethyl)amino]-4-oxobutanoic acid methyl ester
[Compound of formula I where R=NMe_2; X=Cl; W=-NHTBu; R^3=CH_2COOMe; R^4=H]

[7S-(7α,10aα)]-4-[[9-(Aminocarbonyl)-3-chloro-4,7- bis (dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8, 10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-amino]-3-(dimethyl amino)-4-oxobutanoic acid methyl ester
[Compound of formula I where R=NMe_2; X=Cl; W=NMe_2; R^3=CH_2COOMe; R^4=H]

[7S-(7α,10aα)]-γ-[[[9-(Aminocarbonyl)-3-chloro-4,7- bis (dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8, 10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-amino]carbonyl]-1-pyrrolidinebutanoic acid methyl ester
[Compound of formula I where R=NMe_2; X=Cl; W=pyrrolidin-1-yl; R^3=CH_2CH_2COOMe; R^4=H]

[7S-(7α,10aα)]-1-[2-[[9-(Aminocarbonyl)-3-chloro-7-(dimethyl amino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a, 11-tetra hydroxy-10,12-dioxo-2-naphthacenyl]amino]-1-methyl-2-oxo ethyl] proline methyl ester
[Compound of formula I where R=H; X=Cl; W=-2-methoxycarbonyl-pyrrolidin-1-yl; R^3=CH_3; R^4=H]

[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-7-(dimethyl amino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetra hydroxy-10,12-dioxo-2-naphthacenyl]-α-(4-hydroxyphenyl)-6-methyl-2,6-diazabicyclo-[2.1.1]heptane-2-acetamide
[Compound of formula I where R=H; X=Cl; W=6-methyl-2,6-diazabicyclo[2.1.1]heptan-2-yl; R^3=hydroxyphenyl; R^4=H]

[4S-(4α,12aα)]-8-Chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[1-(4-methoxy-1-piperazinyl)-4-pentenoyl]amino]-1,11-dioxo-2-naphthacene carboxamide
[Compound of formula I where R=H; X=Cl; W=4-methoxypiperazin-1-yl; R^3=$CH_2CH_2CH=CH_2$; R^4=H]

[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-7-(dimethyl amino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetra hydroxy-10,12-dioxo-2-naphthacenyl]-α-4-pyridyl-5-azabicyclo[2.1.1]hexan-5-acetamide
[Compound of formula I where R=H; X=Cl; W=azabicyclo[2.1.1]hex-1-yl; R^3=4-pyridyl; R^4=H]

[0014] This invention also provides the following compounds having formula III as shown above with the values as indicated

[4S-(4α,12aα)]-9-[(α-Bromocyclobutylacetyl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene carboxamide
[Compound of formula III where R=NMe_2; X=Cl; R^4=H; R^3=cyclobutyl; Y=Br]

[4S-(4α 12aα)]-9-[(α-Bromo-α-cyclopropyl propionyl)-amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,-6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
[Compound of formula III where R=NMe_2; X=Cl; R^3=cyclopropyl; R^4=Me; Y=Br]

[4S- (4α.12aα)]-9-[(α-Bromo-(2-furyl)propionyl)amino] -8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
[Compound of formula III where R=NMe_2; X=Cl; R^3=furanylmethyl; R^4=H; Y=Br]

[4S-(4α.12aα)]-9-[(α-Bromo-(3-methoxycarbony.propionyl))amino]-8-chloro-4.7-bis(dimethylamino)-1,4 4a.5.5a. 6,11,12a-octahydro-3.10.12.12a-tetrahydroxy-1.11-dioxo-2-naphthacenecarboxamide
[Compound of formula III where R=NMe_2; X=Cl; R^3=methoxylcarbonylmethyl; R^4=H; Y=Br]

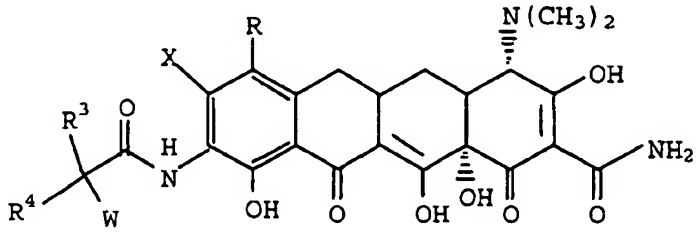
[4S-(4α,12aα)]-9-[(α-Bromo(4-methoxycarbonylbutyryl)) amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a. 6, 11,12a-octahydro-3.10.12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
[Compound of formula III where R=NMe_2; X=Cl; R^3=methoxylcarbonylethyl; R^4=H; Y=Br]

[4S-(4α,12aα)]-9-[(2-Bromo-4-pentenoyl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3, 10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide
[Compound of formula III where R=H; X=Cl; R^3=-$CH_2CH=CH_2$; R^4=H; Y=F;hydrobromide salt]

[4S-(4α,12aα)]-9-[((4-Pyridyl)-α-bromoacetyl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene carboxamide hydrobromide
[Compound of formula III where R=H; X=Cl; R^3=4-pyridyl; R^4=H; Y=Br; hydrobromide salt]

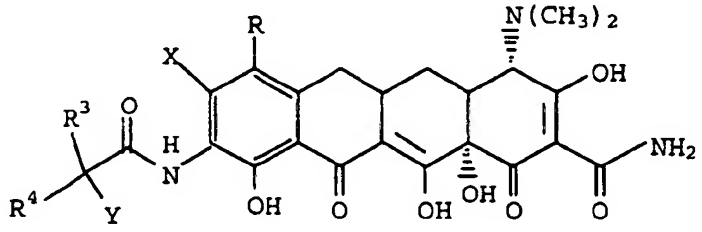
[0015] This invention also provides processes for preparing the compounds of the invention which comprise one of the following:

A) a method of producing a compound of formula (I), or its organic and inorganic salts or metal complexes of the formula:



I

as defined above, which comprises reacting a 9-[(haloacyl)amido]-7-(substituted)-8-(substituted)-6-demethyl-6-deoxytetracycline, or its organic and inorganic salt or metal complex, of the formula (III):

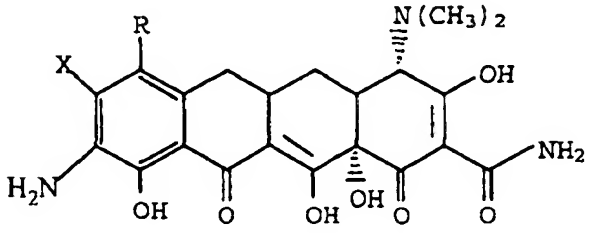


III

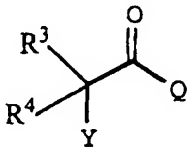
as defined above, with a nucleophile of the formula WH, wherein W is as defined above, in a polar protic or a polar-

aprotic solvent and in an inert atmosphere:

B) a method of producing a compound of formula (III), or its organic and inorganic salt or metal complex, as defined above, which comprises reacting a 9-amino-7-(substituted)-8-(substituted)-6-demethyl-6-deoxytetracycline, or its organic and inorganic salt or metal complex, of the formula:

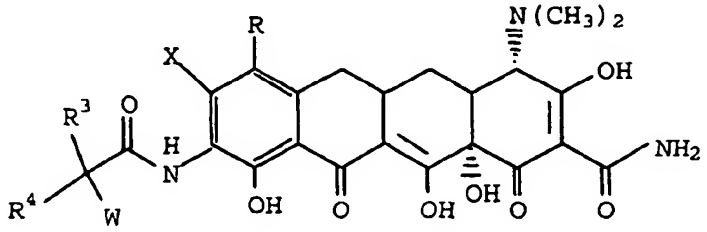


with a straight or branched haloacyl halide of the formula:



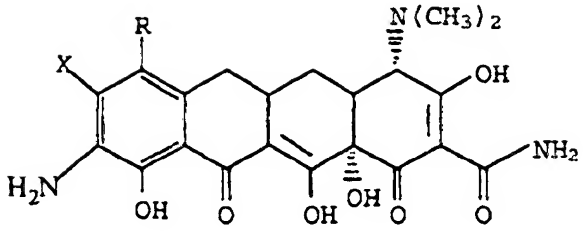
wherein Y, R^3 and R^4 are as defined above and Q is halogen selected from bromine, chlorine, iodine and fluorine, in an inert solvent, in a polar protic solvent and in the presence of a base;

C) a method of producing a compound, or its organic and inorganic salt or metal complex, of the formula:

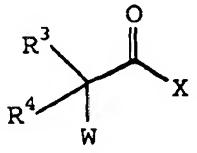


I

as defined above, which comprises reacting a 9amino-7-(substituted)-8-(substituted)-6-demethyl-6-deoxytetracycline, or its organic and inorganic salt or metal complex, of the formula:

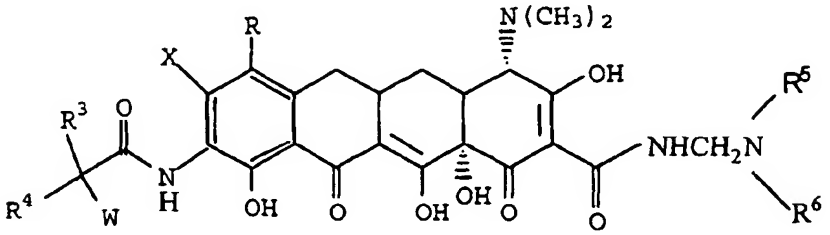


with a straight or branched acid chloride of the formula:



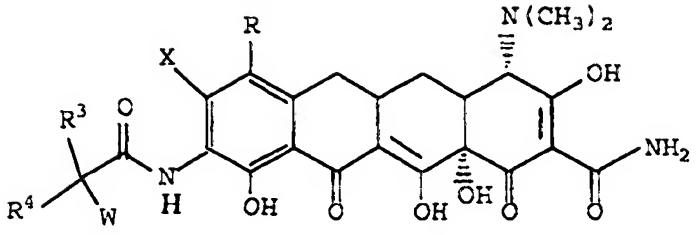
wherein R^3,R^4 and W are as defined above and X is halogen selected from bromine, chlorine, iodine and fluorine, in a suitable acid scavenger and suitable solvent;
and

D) a method of producing a compound of the formula:



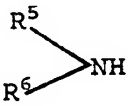
II

as defined above. which comprises reacting a 9[(substituted glycyl)amido]-7-(substituted)-8-(sub-stituted)-6-demethyl-6-deoxytetracycline of the formula:



(I)

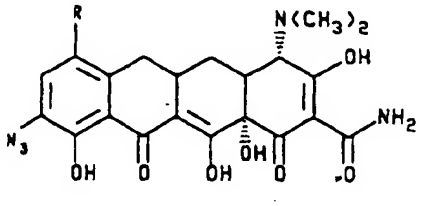
as defined above with a primary amine of the formula R^5NH_2 or a secondary amine of the formula



wherein R^5 and R^6 are as defined above, in the presence of formaldehyde.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0016] The novel compounds of the present invention may be readily prepared in accordance with the following schemes

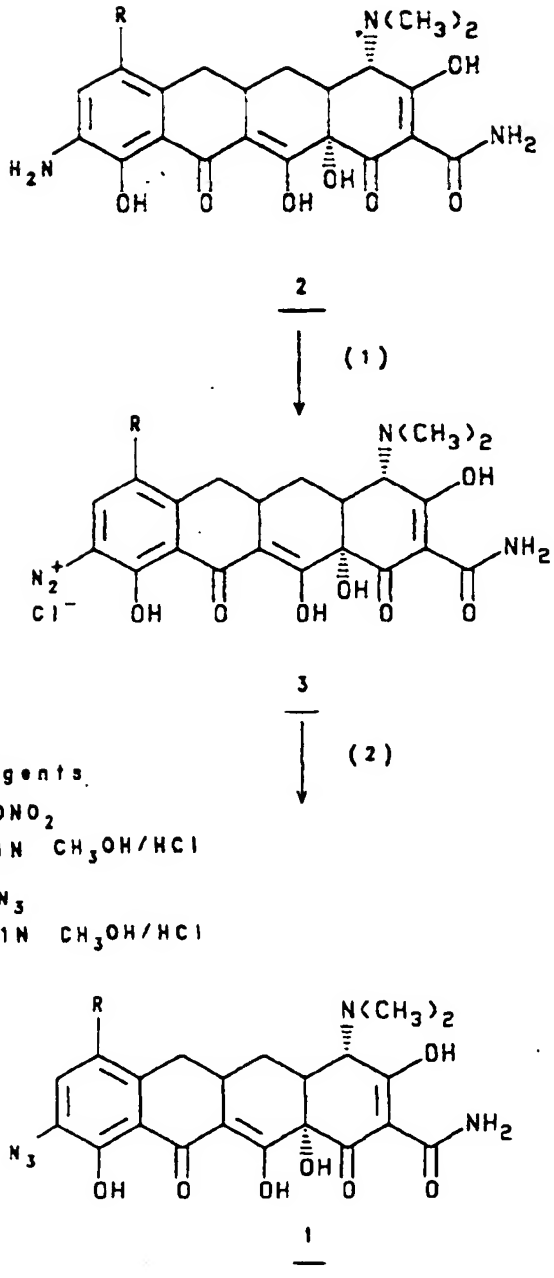


1

1a. R = NR^2R^3, $R^2 = R^3$
1b. R = NR^2R^3, $R^2 \neq R^3$
1c. R = X, X = halogen, hydrogen

[0017] The starting 9-azido-7-(substituted)-6-demethyl-6-deoxytetracycline, 1, described in formula 1 is prepared according to Scheme I.

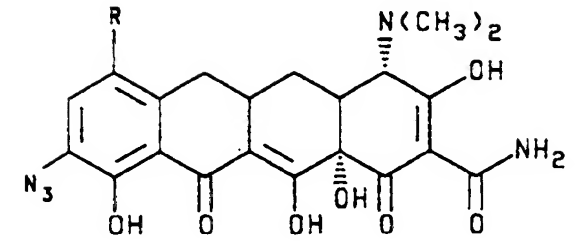
Scheme 1



[0018] In accordance with Scheme I, 9-amino-7-(substituted)-6-demethyl-6-deoxytetracycline 2, or the mineral acid or halide salt, dissolved in 0.1N methanolic hydrogen chloride, is treated for from 5 minutes to 8 hours at from -20°C to +45°C with an excess of n-butyl nitrite to give a 9-diazonium-7-(substituted)-6-demethyl-6-deoxytetracycline, 3, or the mineral acid or halide salt. The formed diazonium compound, 3, or the mineral acid or halide salt, dissolved in 0.1 N methanolic hydrogen chloride, is treated for 5 minutes to 8 hours at from -5°C to +50°C with one equivalent of sodium azide to give the corresponding 9-azido-7-(substituted)-6-demethyl-6-deoxytetracycline, 1, or the mineral acid or halide

salt.

Scheme 2



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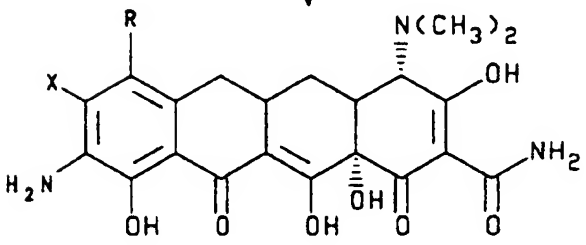
(3)



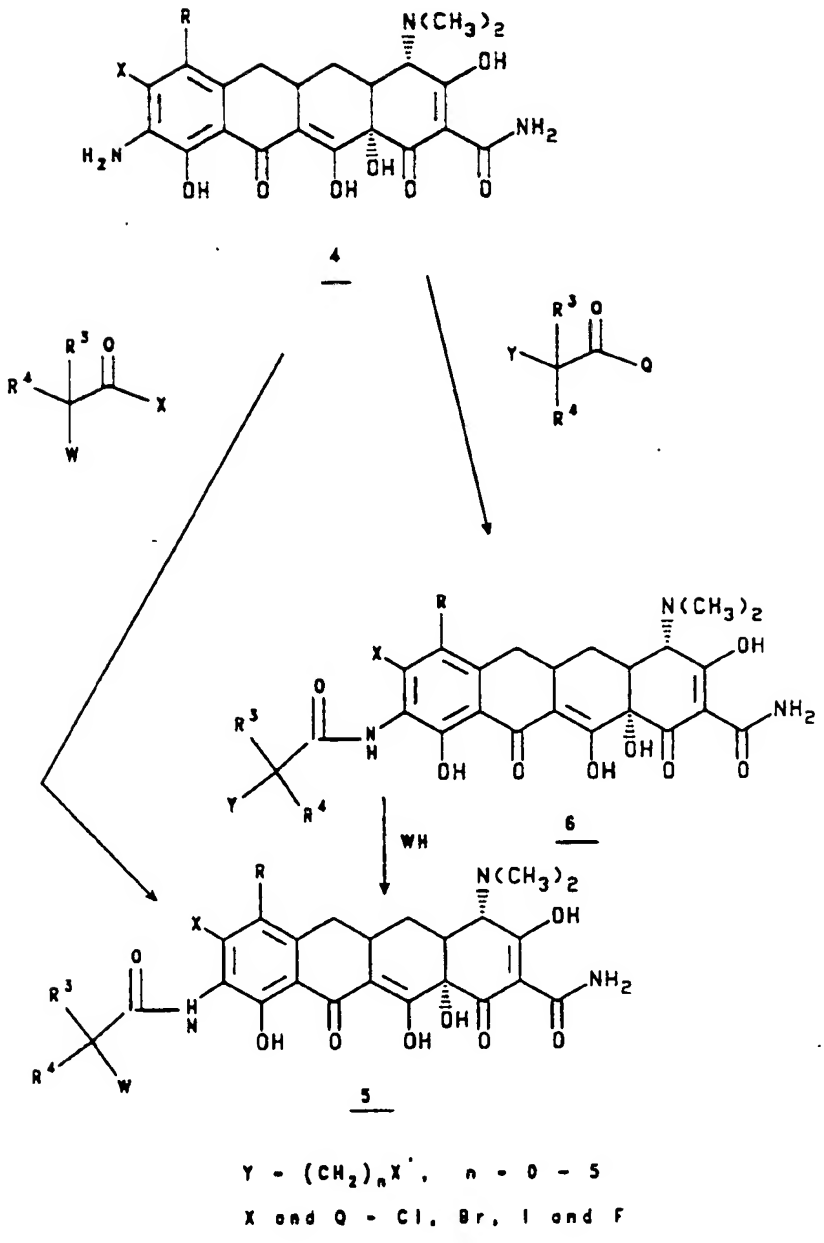
4

3. Strong acid
(HCl, H_2SO_4, CF_3SO_3H, CH_3SO_3H, HI, HF and HBr)

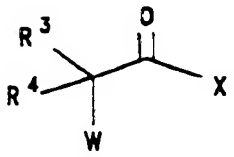
[0019] In accordance with Scheme II, a 9-azido-7-(substituted)-6-demethyl-6-deoxytetracycline, 1, or the mineral acid or halide salt, is treated for from 5 minutes to 12 hours at from -5°C to 40°C with a strong acid, such as sulfuric acid, hydrochloric acid, methanesulfonic acid, trifluoromethanesulfonic acid, hydrobromic, hydroiodic, or hydrogen fluoride to produce a 9-amino-7-(substituted)-8-(substituted)-6-demethyl-6-deoxytetracycline, 4, or the mineral acid or halide salt.

[0020] The 9-amino-7-(substituted)-8-(substituted)-6-demethyl-6-deoxytetracycline, 4, or the mineral acid or halide salt, can be further converted as described in Scheme III.

Scheme 3



[0021] In accordance with Scheme III, a 9-amino-7-(substituted)-8-(substituted)-6-demethyl-6-deoxytetracycline, 4, or the mineral acid or halide salt, is treated at room temperature for from 0.5 - 2 hours with an acid chloride of the formula:

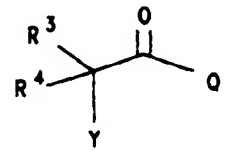


wherein R^3, R^4, W and X are defined hereinabove; in the presence of a suitable acid scavenger, in a suitable solvent, to form the corresponding 9-[(substituted glycyl)amido]-7-(substituted)-8-(substituted)-6-demethyl-6-deoxytetracycline, 5, or the mineral acid or halide salt.

[0022] The acid scavenger is selected from sodium bicarbonate, sodium acetate, pyridine, triethylamine, N,O-bis(trimethylsilyl) acetamide, N,O-bis(trimethylsilyl)trifluoroacetamide, potassium carbonate, a basic ion exchange resin or equivalent thereof.

[0023] The solvents are selected from water, tetrahydrofuran, N-methylpyrrolidone, 1,3-dimethyl-2-imidazolidinone, hexamethylphosphoramide, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)pyrimidinone, 1,2-dimethoxyethane or equivalent thereof.

[0024] Alternatively, in accordance with Scheme III, 9-amino-7-(substituted)-8-(substituted)-6-demethyl-6-deoxytetracycline, 4, or the mineral acid or halide salt, is treated with a straight or branched chain α-haloacyl halide of the formula:



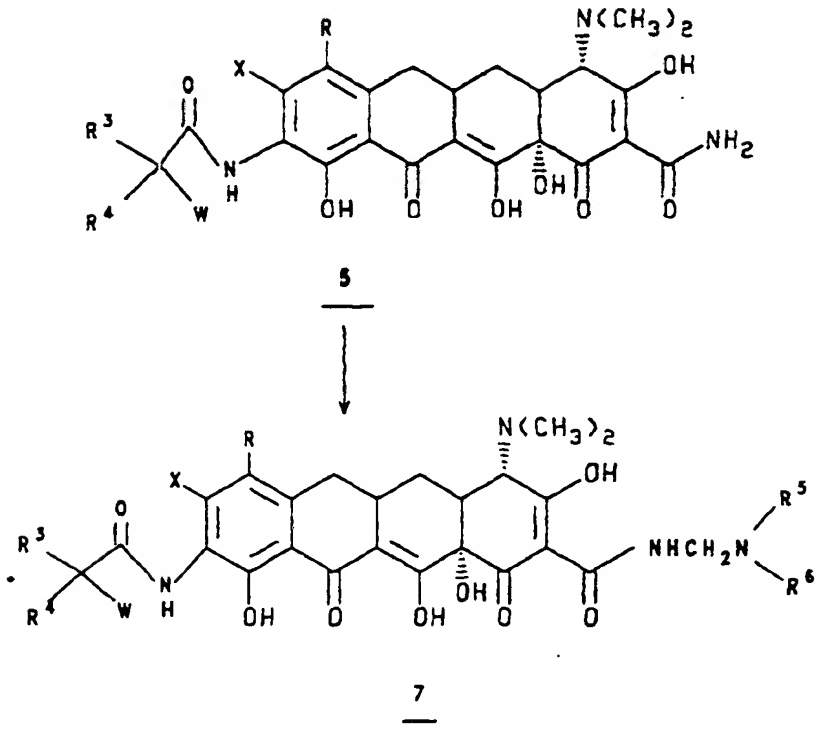
wherein R^3, R^4 and Y are defined hereinabove and Q is halogen selected from bromine, chlorine, fluorine and iodine, such as bromoacetyl bromide, chloroacetyl chloride, 2-bromopropionyl bromide or equivalent thereof; in the presence of a suitable acid scavenger, in a suitable of solvent, to form the corresponding 9-[(haloacyl)amido]-7-(substituted)-8-(substituted)-6-demethyl-6-deoxytetracycline, 6, or the mineral acid or halide salt.

[0025] The halogen, Y, and halide, Q, in the haloacyl halide can be the same or different halogen and are selected from bromine, chlorine, iodine and fluorine; Y is $(CH_2)_nX'$, n= 0-5 and X' is a halogen.

[0026] The acid scavenger and suitable solvent are as defined hereinabove.

[0027] The 9-[(haloacyl)amido]-7-(substituted)-8-(substituted)-6-demethyl-6-deoxytetracycline, 6, or mineral acid or halide salt, is treated, under an inert atmosphere of nitrogen, argon or helium, with nucleophiles of the formula, WH, where W is defined hereinabove, such as amines or substituted amines or equivalents thereof, in a suitable solvent to form the corresponding 9-[(substituted glycyl)amido]-7-(substituted)-8-(substituted)-6-demethyl-6-deoxytetracycline, 5, or mineral acid or halide salt.

Scheme 4



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[0028] In accordance with Scheme IV, compound 5 is selectively N-alkylated in the presence of formaldehyde and either a primary amine of the formula R^5NH_2 such as methylamine, ethylamine, benzylamine, methyl glycinate, (L or D)lysine, (L or D)alanine or their substituted congeners; or a secondary amine of the formula R^5R^6NH such as morpholine, pyrrolidine, piperidine or their substituted congeners to give the corresponding Mannich base adduct, 7.

[0029] The 9-[(substituted glycyl)amido]-7-(substituted)-8-(substituted)-6-demethyl-6-deoxytetracyclines may be obtained as metal complexes such as aluminum, calcium, iron, magnesium, manganese and complex salts; inorganic and organic salts and corresponding Mannich base adducts using methods known to those skilled in the art (Richard C. Larock, Comprehensive Organic Transformations, VCH Publishers, 411-415. 1989). Preferably, the 7-(substituted)-8-(substituted)-9-(substituted)-6-demethyl-6-deoxytetracyclines are obtained as inorganic salts such as hydrochloric, hydrobromic, hydroiodic, phosphoric, nitric or sulfate; or organic salts such as acetate, benzoate, citrate, cysteine or other amino acids, fumarate, glycolate, maleate, succinate, tartrate, alkylsulfonate or arylsulfonate. Depending on the stoichiometry of the acids used, the salt formation occurs with the C(4)-dimethylamino group (1 equivalent of acid) or with both the C(4)-dimethylamino or the W group (2 equivalents of acid). The salts are preferred for oral and parenteral administration.

[0030] Some of the compounds of the hereinbefore described Schemes have centers of asymmetry at the carbon bearing the W substituent. The compounds may, therefore, exist in at least two (2) stereoisomeric forms. The present invention encompasses all stereoisomers of the compounds whether free from other stereoisomers or admixed with stereoisomers in any proportion of enantiomers. The absolute configuration of any compound may be determined by conventional X-ray crystallography.

[0031] The stereochemistry centers on the tetracycline unit (i.e., C-4, C-4a, C-5a and C-12a) remain intact throughout the reaction sequences.

BIOLOGICAL ACTIVITY

Methods for In Vitro antibacterial evaluation

(Table I)

[0032] The minimum inhibitory concentration (MIC), the lowest concentration of the antibiotic which inhibits growth of the test organism, is determined by the agar dilution method using 0.1 ml Muller-Hinton II agar (Baltimore Biological Laboratories) per well. An inoculum level of 1-5 x 10^5 CFU/ml, and a range of antibiotic concentrations (32-0.004 microgram/ml) is used. MIC is determined after the plates are incubated for 18 hours at 35°C in a forced air incubator. The test organisms comprise genetically defined strains that are sensitive to tetracycline and resistant strains that are insensitive to tetracycline, either by preventing the antibiotic from interacting with bacterial ribosomes (tetM) or by a tetK encoded membrane protein which confers tetracycline resistance by energy-dependent efflux of the antibiotic from the cell.

Testing Results

[0033] The claimed compounds exhibit antibacterial activity against a spectrum of tetracycline sensitive and resistant Gram-positive and Gram-negative bacteria, especially, strains of E. coli, S. aureus and E. faecalis, containing the tetM resistance determinants (Table I). Notable is 8-chloro-9-(N,N-dimethylglycylamido)-6-demethyl-6-deoxytetracycline, as shown in Table I, which has good in vitro activity against tetracycline resistant strains containing the tetM resistance determinant (such as S. aureus UBMS 88-5, S.aureus UBMS 90-1 and 90-2. E. coli UBMS 89-1 and 90-4) and is equally as effective as minocycline against susceptible strains.

[0034] Most importantly, these compounds also exhibit antibacterial activity against bacteria that contain an active efflux resistant mechanism as in tetA, tetB, or tetK (i.e., E. coli UBMS 88-1, E. coli PRPI tetA, E. coli Me4100 TN10-tetB, and S. aureus UBMS 88-7 tetK).

[0035] As can be seen from Table I, compounds of the invention may be used to prevent or control important mammalian and veterinary diseases such as diarrhea, urinary tract infections, infections of skin and skin structure, ear, nose and throat infections, wound infections, mastitis and the like.

COMPOUND LEGEND FOR TABLES

[0036]

A [4S-(4α,12aα)]-8-Chloro-4-(dimethylamino)-9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,-6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide disulfate.

B [4S-(4α,12aα)]-8-Chloro-4,7-(dimethylamino)-9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,6,-11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide.

C [4S-(4α,12aα)]-8-Chloro-4-(dimethylamino)-9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,-6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide.

D [4S-(4α,12aα)]-9-[[(Butylamino)acetyl]amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride.

E [7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1-pyrrolidineacetamide dihydrochloride.

F [4S-(4α,12aα)]-8-Chloro-4-(dimethylamino)-1,4,-4a.5.5a.6.11,12a-octahydro-3.10,12,12a-tetrahydroxy-1.11-dioxo-9-[[(propylamino)acetyl]amino]-2-naphthacenecarboxamide dihydrochloride.

G [4S-(4α,12aα)]-8-Chloro-9-[[(cyclopropylmethylamino)acetyl]amino]-4-(dimethylamino)-1.4.4a.5.-5a,6,11.12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride.

H [4S-(4α,12aα)]-8-Chloro-4-(dimethylamino)-1,4,4a,-5.5a.6.11,12a-octahydro-3,10,12,12a-tetrahydroxy-1.11-dioxo-9-[[(pentylamino)acetyl]amino]-2-naphthacenecarboxamide dihydrochloride.

I [4S-(4α,12aα)]-8-Chloro-4-(dimethylamino)-1,4,4a,-5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(methylamino)acetyl]amino]-2-naphthacenecarboxamide dihydrochloride.

J [7S-(7α,10aα)-N-(9-(Aminocarbonyl)-3-chloro-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1-piperidineacetamide dihydrochloride.

K [4S-(4α 12aα)]-9-[(Chloroacetyl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride.

L Minocycline

M Tetracycline

Table 1

ANTIBACTERIAL ACTIVITY OF 8-(SUBSTITUTED)-9-[(SUBST)TUTED GLYCYL)AMIDO]-6-DEMETHYL-6-DEOXYTETRACYCLINES

MIC (ug/ml)

	Compound												
Organism	A	B	C	D	E	F	G	H	I	J	K	L	M
E. coli UBMS 88-1 Tet B	2	>32	1	2	1	0.5	1	2	1	4	>32	16	>32
E. coli J3272 Tet sens	1	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
E. coli MC 4100 Tet sens.	NT	2	0.25	0.25	0.25	0.12	0.25	0.25	0.25	1	8	0.25	0.5
E. coli PRP1 Tet A	4	16	8	4	2	4	4	2	16	8	>32	4	32
E. coli MC 4100 TN10C Tet B	2	>32	1	1	1	0.5	1	2	1	4	>32	8	>32
E. coli J3272 Tet C	8	16	8	2	1	1	1	2	16	4	>32	2	>32
E. coli UBMS 89-1 Tet M	0.5	32	0.25	0.5	0.25	0.5	0.5	0.5	2	1	8	16	32
E. coli UBMS 89-2 Tet sens.	2	16	1	2	1	1	1	2	2	4	>32	1	2
E. coli J2175	1	32	1	1	1	1	1	2	1	4	>32	1	2
E. coli BAJ9003 IMP MUT	0.25	0.12	0.12	0.25	0.12	0.12	0.12	0.25	0.25	0.25	1	0.06	0.5
E. coli UBMS 90-4 Tet M	1	>32	0.5	1	1	0.5	1	2	1	4	>32	>32	32
E. coli UBMS 90-5	1	32	1	1	1	0.5	1	2	1	4	>32	1	1
E. coli #311 (MP)	0.5	4	0.5	1	0.25	0.5	1	2	2	2	16	1	1
E. coli ATCC 25922	0.5	8	0.5	1	0.25	0.5	1	2	1	2	16	1	1
E. coli J3272 Tet D	0.5	32	0.5	1	0.25	0.25	1	1	1	2	>32	8	>32
S. mariescens FPOR 8733	16	>32	8	16	8	8	8	16	16	>32	>32	8	>32
X. maltophilia NEMC 87210	2	0.5	0.05	4	1	2	4	4	16	4	8	0.25	8
Ps. acruginosa ATCC 27853	>32	>32	>32	>32	32	32	32	>32	16	>32	>32	8	16
S. aureus NEMC 8769	0.06	0.12	0.03	0.5	0.25	0.25	0.5	0.5	0.5	0.5	0.5	0.12	0.25

Table 1 (cont'd)

ANTIBACTERIAL ACTIVITY OF 8-(SUBSTITUTED)-9-[(SUBSTITUTED GLYCYLAMIDO]-6-DEMETHYL-6-DEOXYTETRACYCLINES

MIC (ug/ml)

Organism	Compound												
	A	B	C	D	E	F	G	H	I	J	K	L	M
S. aureus UBMS 88-4	0.12	0.25	0.12	0.5	0.25	0.25	0.5	0.5	0.5	1	0.5	0.12	0.25
S. aureus UBMS 88-5 Tet M	0.25	0.25	2	1	0.25	0.5	0.5	1	0.5	1	1	8	>32
S. aureus UBMS 88-7 Tet K	2	2	0.25	8	2	8	8	4	>32	2	4	0.25	>32
S. aureus UBMS 90-1 Tet M	0.5	0.5	4	2	0.25	0.5	2	2	0.5	2	1	8	>32
S. aureus UBMS 90-3	0.12	0.12	0.12	0.12	0.12	0.5	0.12	0.25	0.5	0.25	0.25	0.06	0.25
S. aureus UBMS 90-2 Tet M	0.5	0.25	1	0.5	0.25	0.25	0.5	0.25	0.5	0.5	0.5	4	32
S. aureus IVES 2943	4	4	4	16	4	16	16	8	>32	2	4	4	>32
S. aureus ROSE (MP)	16	8	1	16	8	16	32	8	>32	4	4	1	>32
S. aureus SMITH (MP)	0.25	0.12	0.12	0.5	0.25	0.25	0.5	0.5	0.5	1	0.5	0.12	0.25
S. aureus IVES 1 983	4	4	4	8	4	8	16	4	>32	4	4	4	>32
S. aureus ATCC 29213	0.03	0.25	0.25	0.5	0.25	0.25	0.25	0.5	0.5	0.5	0.5	0.12	0.25
S. hemolyticus AVHAH 88-3	1	0.5	0.5	8	2	4	8	4	2	4	4	0.25	1
Enterococcus 12201	0.25	0.12	8	0.5	0.25	0.25	0.25	0.25	0.5	0.5	2	8	>32
E. faecalis ATCC 29212	0.12	0.12	0.5	0.25	0.12	0.12	0.25	0.12	0.25	0.25	0.5	4	16

[0037] When the compounds are employed as antibacterials, they can be combined with one or more pharmaceu-

tically acceptable carriers, for example, solvents, diluents and the like, and may be administered orally in such forms as tablets, capsules, dispersible powders, granules, or suspensions containing, for example, from about 0.05 to 5% of suspending agent, syrups containing, for example, from about 10 to 50% of sugar, and elixirs containing for example, from about 20 to 50% ethanol and the like, or parenterally in the form of sterile injectable solutions or suspensions containing from about 0.05 to 5% suspending agent in an isotonic medium. Such pharmaceutical preparations may contain, for example, from about 25 to about 90% of the active ingredient in combination with the carrier, more usually between about 5% and 60% by weight.

[0038] An effective amount of compound from 2.0 mg/kg of body weight to 100.0 mg/kg of body weight should be administered one to five times per day via any typical route of administration including but not limited to oral, parenteral (including subcutaneous, intravenous, intramuscular, intrasternal injection or infusion techniques), topical or rectal, in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

[0039] These active compounds may be administered orally as well as by intravenous, intramuscular, or subcutaneous routes. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvants customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

[0040] The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules. Oral administration of the compounds is preferred.

[0041] These active compounds may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in glycerol, liquid, polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

[0042] The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserve against the contaminating action of microorganisms such as bacterial and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oil.

[0043] The invention will be more fully described in conjunction with the following specific examples which are not be construed as limiting the scope of the invention.

Example 1

[7S-(7alpha, 10alpha)]-9- (Aminocarbonyl)-4.7-bis(dimethyl amino)-5.5a.6.6a,7,10,10a,12-octahydro-1.8.10a.11-tetra hydroxy-10,12-dioxo-2-naphthacenediazonium chloride sulfate (1:1)

[Compound 3 where R=NMe_2; chloride sulphate salt]

[0044] To a 0°C solution of 3.0 g of 9-amino-4,7-bis(dimethyl amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra hydroxy-1.11-dioxo-2-naphthacenecarboxamide sulfate, dissolved in 100 ml of 0.1N methanolic hydrogen chloride is added, dropwise, 6.6 ml of butyl nitrite. The reaction is stirred at 0°C for 1 hour, poured into 400 ml of diethyl ether, collected and dried to give 2.64 g of the desired product.
MS(FAB): m/z 484 (M + H)

Example 2

[4S-(4α,12aα)]-9-Azido-4,7-bis(dimethylamino)-1,4,4a,5, 5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11 dioxo-2-naphthacenecarboxamide hydrochloride (1:1)

[Compound 1 where R=NMe_2; hydrochloride salt]

[0045] To a room temperature solution of 2.64 g of product from Example 1 dissolved in 84 ml of 0.1N methanolic hydrogen chloride is added 0.353 g of sodium azide. The mixture is stirred at room temperature for 4 hours, poured into 500 ml of diethyl ether and collected to give 2.5 g of the desired product.
IR(KBr): 2080 cm^{-1}.

Example 3

9-Amino-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6, 11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2 naphthacenecarboxamide sulfate

[Compound 4 wherein R=NMe_2; X=Cl; sulphate salt]

[0046] One gram of product from Example 2 is added to 10 ml of 0°C concentrated sulfuric acid. The reaction is stirred at 0°C for 1.5 hours, poured into 500 ml of diethyl ether, collected and dried to give 1.1 g of the desired product.
MS(FAB): m/z 507 (M + H).

Example 4

[4S-(4α,12aα)]-9-Amino-4,7-bis(dimethylamino)-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

[Compound 4 where R=NMe_2; X=H]

[0047] The title compound is prepared by the procedure of Example 3 using the product of Example 2 and liquid hydrogen fluoride.

Example 5

9-Amino-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene carboxamide hydrochloride (1:1)

[Compound 4 where R=H; X=Cl; hydrochloride salt]

[0048] To 10 ml of concentrated hydrochloric acid at 0°C is added 0.20 g of 9-azido-6-demethyl-6-deoxytetracycline hydrochloride prepared by the procedure described in J. Am. Chem. Soc., 84: 1426-1430. The reaction is stirred at 0°C for 1 1/2 hours and concentrated in vacuo to give 0.195 g of the desired product.
MS(FAB): m/z 464 (M + H).

Example 6

[4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-8-fluoro-1,4,4a,5, 5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene carboxamide

[Compound 4 where R=H; X=H]

[0049] The title compound is prepared by the procedure of Example 3 using 9-azido-6-demethyl-6-deoxytetracycline and liquid hydrogen fluoride.

Example 7

[4S-(4α,12aα)]-9-Amino-4,7-bis(dimethylamino)-1,4,4a,5,5a, 6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-8-[[(trifluoromethyl)sulfonyl]oxy]-2-naphthacenecarboxamide

[Compound 4 where R=NMe_2; X=OSO_2CF_3]

[0050] The title compound is prepared by the procedure of Example 3 using 9-azido-4,7-bis(dimethylamino)-6-demethyl-6-deoxytetracycline and trifluoromethanesulfonic acid.

Example 8

[4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a,tetrahydroxy-1,11-dioxo-8-[[(trifluoromethyl)sulfonyl]oxy]-2-naphthacenecarboxamide

[Compound 4 where R=H; X=-OSO_2CF_3]

[0051] The title compound is prepared by the procedure of Example 3 using 9-azido-4-(dimethylamino)-6-demethyl-6-deoxytetracycline and trifluoromethanesulfonic acid.

Example 9

[4S-(4α,12aα)]-9-[(Chloroacetyl)aminol-8-chloro-4,7-bis (dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

[Compound of Formula III where R=NMe_2; X=Cl; R^3=H; R^4=H; Y=Cl]

[0052] A well-stirred cold solution of 1.0 g of product from Example 3, 2 ml of 1,3-dimethyl-2-imidazolidinone and 1.0 g of sodium bicarbonate is treated with 0.30 ml of chloroacetyl chloride. The solution is stirred at 25°C for 30 minutes, filtered and the filtrate added dropwise to 500 ml of diethyl ether to afford 1.0 g of yellow product.

Example 10

[4S-(4α,12aα)]-9-[(Bromoacetyl)amino]-8-chloro-4,7-bis (dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

[Compound of Formula III where R=NMe_2; X=Cl; R^3=H; R^4=H; Y=Br]

[0053] A well-stirred cold solution of 1.0 g of product from Example 3, 2 ml of 1,3-dimethyl-2-imidazolidinone and 1.0 g of sodium bicarbonate was treated with 0.36 ml of bromoacetyl bromide. The solution was stirred at 25°C for 30 minutes, filtered and the filtrate added dropwise to 500 ml of diethyl ether to afford 0.7 g of yellow product.

Example 11

[4S-(4α,12aα)]-9-[(α-Bromopropionyl)amino]-8-chloro-4,7-bis (dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a -tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

[Compound of Formula III where R=NMe_2; X=Cl; R^3=H; R^4=Me; Y=Br]

[0054] A well-stirred cold solution of 1.0 g of product from Example 3, 2 ml of 1,3-dimethyl-2-imidazolidinone and 1.0 g of sodium bicarbonate was treated with 0.42 ml of bromopropionyl bromide. The solution was stirred at 25°C for 30 minutes, filtered and the filtrate added dropwise to 500 ml of diethyl ether to afford 1.0 g of yellow product.

[0055] Substantially following the method, described in detail herein above in Example 10, the compounds of the invention listed in Examples 12-19 are prepared.

Example 12

[4S-(4α,12aα)]-9-[(α-Bromocyclobutylacetyl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10, 12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

[Compound of Formula III where R=NMe_2; X=Cl; R^4=H; R^3=cyclobutyl; Y=Br]

Example 13

[4S-(4α,12aα)]-9-[(α-Bromophenylacetyl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12, 12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

[Compound of Formula III where R=NMe_2; X=Cl; R^4=Ph; R^3=H; Y=Br]

Example 14

[4S-(4α,12aα)]-9-[(α-Bromo-α-cyclopropylpropionyl)amino]-8-chloro-4,7-big(dimethylamino)-1,4,4a,5,5a,-6,11,12a-octa hydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene carboxamide

[Compound of Formula III where R=NMe_2; X=Cl; R^3=cyclopropyl; R^4=Me; Y=Br]

Example 15

[4S-(4α,12aα)]-9-[(α-Bromo-3,3-dimethylbutyryl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octa hydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene carboxamide

[Compound of Formula III where R=NMe_2; X=Cl; R^3=Isopropyl; R^4=H; Y=Br]

Example 16

[4S(4α,12aα)]-9-[(α-Bromo(2,4-difluorophenyl)acetyl)amino] -8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octa hydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene carboxamide

[Compound of Formula III where R=NMe_2; X=Cl; R^3=2,4-difluorophenyl; R^4=H; Y=Br]

Example 17

[4S-(4α,12aα)]-9-[(α-Bromo-2-(2-furyl)propionyl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octa hydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene carboxamide

[Compound of Formula III where R=NMe_2; X=Cl; R^3=furanylmethyl; R^4=H; Y=Br]

Example 18

[4S-(4α,12aα)]-9-[(α-Bromo-(3-methoxycarbonyl-propionyl)) amino]-8-chloro-4,7-bis(dimethylamino)-1.4,4a,5,5a. 6,11.12a -octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

[Compound of Formula III where R=NMe_2; X=Cl; R^3=methoxycarbonylmethyl; R^4=H; Y=Br]

Example 19

[4S-(4α,12aα)]-9-[(α-Bromo-(4-methoxycarbonylbutyryl)) amino]-8-chloro-4,7-bis(dimethylamino)-1.4,4a,5,5a. 6,11.12a -octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

[Compound of Formula III where R=NMe_2; X=Cl;

R^3=methoxycarbonylethyl; R^4=H; Y=Br]

Example 20

[4S-(4α,12aα)]-9-[(Bromoacetyl)amino]-4,7-bis(dimethyl amino)-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

[Compound of Formula III where R=NMe_2; X=F; R^3=H; R^4=H; Y=Br]

[0056] The title compound is prepared by the procedure of Example 10 using the product from Example 4.

Example 21

[4S-(4α,12aα)]-9-[(Bromoacetyl)amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra hydroxy-1,11-dioxo-8-[[(trifluoromethyl)sulfonyl]oxy]-2-naphthacenecarboxamide

[Compound of Formula III where R=NMe_2; X=OSO_2CF_3; R^3=H; R^4=H; Y=Br; hydrochloride salt]

[0057] The title compound is prepared by the procedure of Example 10 and using the product from Example 7.

Example 22

[4S-(4α,12aα)]-9-[(Chloroacetyl)amino]-8-chloro-4-(dimethyl amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra hydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride

[Compound of Formula III where R=H; X=Cl; R^3=H; R^4=H; Y=Cl; hydrochloride salt]

[0058] A 25°C solution of 1.247 g of product from Example 5, 12 ml of DMPU and 6 ml of acetonitrile is treated with 0.564 g of chloroacetyl chloride. The mixture is stirred for 45 minutes and added dropwise to a mixture of 80 ml of 2-propanol and 400 ml of diethyl ether. The resultant yellow solid is filtered and washed several times with diethyl ether and dried in vacuo to give 1.25 g of product.
MS (FAB) = m/z 540 (M + H)

Example 23

[4S-(4α,12aα)]-9-[(Bromoacetyl)amino]-8-chloro-4-(dimethyl amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra hydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide

[Compound of Formula III where R=H; X=Cl; R^3=H; R^4=H; Y=Br; hydrobromide salt]

[0059] A 25°C solution of 1.247 g of product from Example 5, 12 ml of DMPU and 6 ml of acetonitrile is treated with 0.62 g of bromoacetyl bromide. The mixture is stirred for 45 minutes and added dropwise to a mixture of 80 ml of 2-propanol and 400 ml of diethyl ether. The resultant yellow solid is filtered and washed several times with diethyl ether and dried in vacuo to give 1.35 g of product.

[0060] Substantially following the method, described in detail herein above in Example 22 or 23, the compounds of the invention listed in Examples 24 - 30 are prepared.

Example 24

[4S-(4α,12aα)]-9-[(2-Chloropropionyl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride

[Compound of Formula III where R=H; X=Cl; R^3=H; R^4=Me; Y=Cl; hydrochloride salt]

Example 25

[4S-(4α,12aα)]-9-[(2-Chlorobutyryl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride

[Compound of Formula III where R=H; X=Cl; R^3=H; R^4=Et; Y=Cl; hydrochloride salt]

Example 26

4S-(4α,12aα)]-9-[[(4-Hydroxyphenyl)-α-chloroacetyl]amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene carboxamide hydrochloride

[Compound of Formula III where R=H; X=Cl; R^3=4-hydroxyphenyl; R^4=H; Y=Cl; hydrochloride salt]

Example 27

[4S-(4α,12aα)]-9-[[(2-Fluorophenyl)-α-bromoacetyl]amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,-12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene carboxamide hydrobromide

[Compound of Formula III where R=H; X=Cl; R^3=2-fluorophenyl; R^4=H; Y=F;hydrobromide salt]

Example 28

[4S-(4α,12aα)]-9-[(2-Bromo-4-pentenoyl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide

[Compound of Formula III where R=H; X=Cl; R^3=-CH_2CH=CH_2; R^4=H; Y=F;hydrobromide salt]

Example 29

[4S-(4α,12aα)]-9-[(α-Bromo-4-phenylbutyryl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11.12a-octahydro-3,10,12, 12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide

[Compound of Formula III where R=H; X=Cl; R^3=2-phenylethyl; R^4=H; Y=Br; hydrobromide salt]

Example 30

[4S-(4α,12aα)]-9-[((4-Pyridyl)-α-bromoacetyl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene carboxamide hydrobromide

[Compound of Formula III where R=H; X=Cl; R^3=4-pyridyl; R^4=H; Y=Br; hydrobromide salt]

Example 31

[4S-(4α,12aα)]-9-[(Bromoacetyl)amino]-4-(dimethylamino)-8-fluoro-1,4,4a,5 5a,6,11,12a-octahydro-3,10,12,12a-tetra hydroxy-1,11-dioxo-2-naphthacenecarboxamide

[Compound of Formula III where R=H; X=F; R^3=H; R^4=H; Y=Br]

[0061] The title compound is prepared by the procedure of Example 10 using the product from Example 6.

Example 32

[4S-(4α,12aα)]-9-[(Bromoacetyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-8-[[(trifluoromethyl)sulfonyl]oxy]-2-naphthacenecarboxamide

[Compound of Formula III where R=H; X=OSO_2CF_3; R^3=H; R^4=H; Y=Br]

[0062] The title compound is prepared by the procedure of Example 10 using the product from Example 8.

Example 33

[4S-(4α,12aα)]-8-Chloro-4-(dimethylamino)-9-[[(dimethyl amino)acetyl]amino]-1,4,4a,5,5a,-6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide disulfate

[Compound of Formula I where R=H; X=Cl; R^3=H; R^4=H; W=NMe_2; disulphate salt]

[0063] A well stirred solution (25°C) of 0.2805 g of product from Example 5, 10 ml of DMPU, 3 ml of acetonitrile and 0.3 g of sodium carbonate is treated with 0.157g of N,N-dimethylaminoacetyl chloride hydrochloride. After 30 minutes, the reaction is filtered and the filtrate is added dropwise to 300 ml of diethyl ether. Concentrated sulfuric acid is added dropwise and a yellow solid precipitated. The yellow solid is collected, washed well with ether, and dried in vacuo to afford 0.21 g of product:
MS (FAB) = m/z 549 (M + H).

Example 34

[4S-(4α,12aα)]-8-Chloro-4-(dimethylamino)-9-[[(dimethyl amino)acetyllamino]-1,4,4a,5,5a,-6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

[Compound of Formula I where R=H; X=Cl; W=NMe_2; R^3=H; R^4=H]

[0064] A well stirred solution 25°C of 0.20 g of product from Example 5, 3 ml of N-methylpyrrolidone, 1 ml of acetonitrile and 0.2 g of sodium bicarbonate is treated with 0.071g of N,N-dimethylaminoacetyl chloride hydrochloride. After 30 minutes, the reaction is filtered and the filtrate is added dropwise to 200 ml of diethyl ether. The yellow solid is collected, washed well with ether, and dried in vacuo to afford 0.15 g of product:
MS (FAB) – m/z 548 (M + H).

Example 35

[4S-(4α,12aα)1-8-Chloro-4,7-(dimethylamino)-9-[[(dimethyl amino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12. 12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

[Compound of Formula I where R=NMe_2; X=Cl; W=MMe_2; R^3=H; R^4=H]

[0065] A well stirred solution (25°C) of 0.104 g of product from Example 3, 1.5 ml of N-methylpyrrolidone, 0.5 ml of acetonitrile and 0.105 g of sodium bicarbonate is treated with 0.034g of N,N-dimethylaminoacetyl chloride hydrochloride. After 1 hr, the reaction is filtered and the filtrate is added dropwise to 100 ml of diethyl ether. The yellow solid is collected, washed well with ether, and dried in vacuo to afford 0.085 g of product:
MS (FAB) – m/z 591 (M + H).

Example 36

[4S-(4α,12aα)]-9-[[(Butylamino)acetyl]amino]-8-chloro-4.7-bis(dimethylamino)-1,4,4a,5,5a,6,11.12a-octahydro-3,10,12, 12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

[Compound of Formula I where R=NMe_2; X=Cl; W=NHBu; R^3=H; R^4=H]

[0066] A solution of 0.20 g of the product from Example 10, 2 ml of 1,3-dimethyl-2-imidazolidinone and 0.1 ml of n-butylamine is stirred at room temperature for 1 hr and added dropwise to 50 ml of diethyl ether to afford 0.20 g of yellow

color product:
MS (FAB) m/z 620 (M + H)

[0067] Substantially following the method, described in detail herein above in Example 36, the compounds of the invention listed in Examples 37 - 45 are prepared.

Example 37

[4S-(4α,12aα)]-8-Chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a, 6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[(3-methyl cyclobutyl)amino]acetyl]amino]-1,11-dioxo-2-naphthacene carboxamide

[Compound of Formula I where R=NMe_2; X=Cl; W=3-methylcyclobutylamino; R^3=H; R^4=H]

Example 38

[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1H-pyrrole-1-acetamide

[Compound of Formula I where R=NMe_2; X=Cl; W=1H-pyrrol-1-yl; R^3=H; R^4=H]

Example 39

[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis (dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1H-pyrazole-1-acetamide

[Compound of Formula I where R=NMe_2; X=Cl; W=1H-pyrazol-1-yl; R^3=H; R^4=H]

Example 40

[4S-(4α,12aα]-8-Chloro-4,7-bis(dimethylamino)-9-[[[(1,1-dimethylethyl)amino]acetyl]aminol-1,4,4a,5,5a,6,11,12a-octa hydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene carboxamide

[Compound of Formula I where R=NMe_2; X=Cl; W=NHtBu; R^3=H; R^4=H]

Example 41

[4S-(4α,12aα)]-8-Chloro-9-[[(cyclopropylamino)acetyl] amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octa hydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene carboxamide

[Compound of Formula I where R=NMe_2; X=Cl; W=cyclopropylamino; R^3=H; R^4=H]

Example 42

[4S-(4α,12aα)]-8-Chloro-9-[[[(cyclobutyloxy)amino]acetyl] aminol-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,-11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

[Compound of Formula I where R=NMe_2; X=Cl; W=cyclobutyloxyamino; R^3=H; R^4=H]

Example 43

[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis (dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1-pyrrolidineacetamide

[Compound of Formula I where R=NMe_2; X=Cl; W=pyrrolidin-1-yl; R^3=H; R^4=H]

Example 44

[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis (dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,9,10a,11-tetra hydroxy-10,12-dioxo-2-naphthacenyl]-(3-methyl-1-pyrrolidino)acetamide

[Compound of Formula I where R=NMe_2; X=Cl; W=3-methylpyrrolidinl-yl; R^3=H; R^4=H]

Example 45

[4S-(4α,12aα)]-8-Chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a, 6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[(propylamino)]acetyl]amino]-2-naphthacenecarboxamide

[Compound of Formula I where R=NMe_2; X=Cl; W=NHPr; R^3=H; R^4=H]

Example 46

[4S-(4α,12aα)]-8-Chloro-4,7-bis(dimethylamino)-1,4,4a,5, 5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[1-oxo-2-(propylamino)propyl]amino]-2-naphthacenecarboxamide

[Compound of Formula I where R=NMe_2; X=Cl; W=NHPr; R^3=H; R^4=CH_3]

[0068] The title compound is prepared by the procedure of Example 36 using [4S-(4α,12aα)]-9-[(α-bromopropionyl) amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6, 11, 12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide and n-propylamine.

Example 47

[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a, 11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-α-cyclobutyltetrahydro-2H-1,2-isoxazine-2-acetamide

[Compound of Formula I where R=NMe_2; X=Cl; W=tetrahydro-2H-1,2-isoxazin-2-yl; R^3=H;R^4=cyclobutyl]

[0069] The title compound is prepared by the procedure of Example 36 using [4S-(4α,12aα)]-9-[(α-bromocyclobutyl acetyl)amino]-8-chloro-4,7-bis-(dimethylamino)-1,4,4a,5,5a, 6,11,12a-octahydro-3,10,-12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide and tetrahydro-1,2-oxazine.

Example 48

[4S-(4α,12aα)1-8-Chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a, 6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[phenyl[(phenylmethyl)amino]acetyl]amino]-2-naphthacene carboxamide

[Compound of Formula I where R=NMe_2; X=Cl; W=phenyl(phenylmethyl)amino; R^3=H; R^4=H]

[0070] The title compound is prepared by the procedure of Example 36 using [4S-(4α, 12aα)]-9-[(α-bromophenyl acetyl)amino]-8-chloro-4,7-bis(dimethyl-amino)-1,4,4a,5, 5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide and benzylamine.

Example 49

[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a, 11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-α-cyclopropyl-α-methyl-1-azetidine acetamide

[Compound of Formula I where R=NMe_2; X=Cl; W=azetidin-1-yl; R^4=CH_3; R^3=cyclopropyl]

[0071] The title compound is prepared by the procedure of Example 36 using [4S-(4α,12aα)]-9-[(α-bromo-α-cyclo propylpropionyl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide and azetidine.

Example 50

[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-α-(1,1-dimethylethyl)-(3-methyl-4-morpholine)acetamide

[Compound of Formula I where R=NMe_2; X=Cl; W=3-methylmorpholin-4-yl; R^3=tBu; R^4=H]

[0072] The title compound is prepared by the procedure of Example 36 using [4S-(4α,12aα)]-9-[(α-bromo-3,3-dimethyl butyryl)amino]-8-chloro-4,7-bis(di-methylamino)-1,4,4a,5, 5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide and 3-methyl-4-morpholine.

Example 51

[4S-(4α,12aα)]-8-Chloro-9-[[(2,4-difluorophenyl)[(2-phenyl ethyl)amino]acetyl]amino]-4,7-bis(dimethylamino)-1,4,4a,5, 5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

[Compound of Formula I where R=NMe_2; X=Cl; W=(2,4-difluorophenyl) (2-phenylethyl)amino; R^3=H; R^4=H]

[0073] The title compound is prepared by the procedure Example 36 using [4S-(4α,12aα)]-9-[(α-bromo-(2,4-difluoro phenyl)acetyl)amino]-8-chloro-4.7-bis(di-methylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,-12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide and 2-phenethylamine.

Example 52

[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis (dimethylamino)-5.5a.6.6a.7.10.10a.12-octahydro-1.8.10a.11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-α-(methoxy amino)-α-methyl-2-furanacetamide

[Compound of Formula I where R=NMe_2; X=Cl; W=NHOMe;R^3=furan-2-yl; R^4=CH_3]

[0074] The title compound is prepared by the procedure of Example 36 using [4S-(4α,12aα)]-9-[(α-bromo-2-(2-furyl) propionyl))amino]-8-chloro-4,7-bis(di-methylamino)-1,4,4a,5,5a,6,11.12a-octahydro-3,10.12.-12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide and methoxyamine.

[0075] Substantially following the method, described in detail herein above in Example 36, the compounds of the invention listed in Examples 53-54 are prepared from [4S-(4α,12aα)]-9-[(α-bromo-(3-methoxycarbonylpropionyl))amino] -8-chloro-4,7-bis(dimethylamino)-1,4,4a,-5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene carboxamide.

Example 53

[7S-(7α,10aα)]-4-[[9-(Aminocarbonyl)-3-chloro-4,7-bis (dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-amino-3-[(1,1-dimethylethyllaminol-4-oxobutanoic acid methyl ester

[Compound of Formula I where R=NMe_2; X=Cl; W=-NHtBu; R^3=CH_2-CO-OMe; R^4=H]

Example 54

[7S-(7α,10aα)]-4-[[9-(Aminocarbonyl)-3-chloro-4,7-bis (dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-aminol-3-(dimethyl amino)-4-oxobutanoic acid methyl ester

[Compound of Formula I where R=NMe_2; X=Cl; W=NMe_2; R^3=CH_2COOMe; R^4=H]

Example 55

[7S-(7α,10aα)]-γ-[[[9-(Aminocarbonyl)-3-chloro-4,7-bis (dimethylamino)-5.5a.6.6a.7.10.10a.12-octahydro-1.8.10a.11 tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]carbonyl]-3-(1-pyrrolidine)butanoic acid methyl ester

[Compound of Formula I where R=NMe_2; X=Cl; W=pyrrolidin-1-yl; R^3=CH_2COOMe; R^4=H]

[0076] The title compound is prepared by the procedure of Example 36 using [4S-(4α,12aα)]-9-[(α-bromo-(4-methoxy carbonyl)butyryl))amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide and pyrrolidine.

Example 56

[4S-(4α,12aα)]-4,7-Bis(Dimethylamino)-9-[[(dimethylamino) acetyl]amino]-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene carboxamide

[Compound of Formula I where R=NMe_2; X=F; W=NMe_2; R^3=H; R^4=H]

[0077] The title compound is prepared by the procedure of Example 36 using [4S-(4α,12aα)]-9-[(bromoacetyl)amino]-4, 7-bis (dimethylamino) -8-fluoro-1, 4, 4a, -5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene carboxamide and dimethylamine.

Example 57

[4S-(4α,12aα)]-9-[[(Butylamino)acetyl]amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxonaphthacenecarboxamide dihydrochloride

[Compound of Formula I where R=H; X=Cl; W=NHBu; R^3=H; R^4=H]

[0078] A mixture of 0.20 g of the product from Example 22, 0.5 g of n-butylamine and 3 ml of DMPU, under argon, is stirred at room temperature for 2 h.
The excess n-butylamine was removed in vacuo and the solids filtered. The filtrate is diluted with a small amount of methanol and the solution added dropwise to a mixture of 10 ml of 2-propanol and 120 ml of diethyl ether. The solution is treated dropwise with 1.0 M hydrogen chloride - diethyl ether solution to afford a yellow solid. The resulting solid is collected and dried in vacuo to afford 0.175 g of product:
MS (FAB) – m/z 576 (M + H)

[0079] Substantially following the method described in detail herein above in Example 57, the compounds of the invention listed below in Examples 58 - 66 are prepared.

Example 58

[4S-(4α,12aα)]-8-Chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(propylamino)acetyl]amino]-2-naphthacenecarboxamide dihydrochloride

[Compound of Formula I where R=H; X=Cl; W=NHPr; R^3=H; R^4=H]

Example 59

[4S-(4α,12aα)]-8-Chloro-4-(dimethylamino)-1,4,4a,5,5a,6, 11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(pentylamino)acetyl]amino]-2-naphthacenecarboxamide dihydrochloride

[Compound of Formula I where R=H; X=Cl; W=phenylamino; R^3=H; R^4=H]

Example 60

[4S-(4α,12aα)]-8-Chloro-4-(dimethylamino)-1,4,4a,5,5a,6, 11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(methylamino)acetyl]amino]-2-naphthacenecarboxamide dihydrochloride

[Compound of Formula I where R=H; X=Cl; W=NHMe; R^3=H; R^4=H]

Example 61

[4S-(4α,12aα)]-8-Chloro-9-[[(cyclopropylmethyl)amino)acetyl] amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene carboxamide dihydrochloride

[Compound of Formula I where R=H; X=Cl; W=cyclopropylmethylamino; R^3=H; R^4=H]

Example 62

[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-7-(dimethyl amino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1-pyrrolidine acetamide dihydrochloride

[Compound of Formula I where R=H; X=Cl; W=pyrrolidin-1-yl; R^3=H; R^4=H]

Example 63

[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-7-(dimethyl amino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1-piperidine acetamide dihydrochloride

[Compound of Formula I where R=H; X=Cl; W=piperidin-1-yl;R^3=H; R^4=H]

Example 64

7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-7-(dimethyl amino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-5-azabicyclo [2.1.1]hexane-5-acetamide dihydrochloride

[Compound of Formula I where R=H; X=Cl; W=azabicyclo[2.1.1]hex-5-yl; R^3=H; R^4=H]

Example 65

[4S-(4α,12aα)]-8-Chloro-9-[[(cyclobutylamino)acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12, 12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride

[Compound of Formula I where R=H; X=Cl; W=cyclobutylamino; R^3=H; R^4=H]

Example 66

[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-7-(dimethyl amino)-5,5a, 6, 6a,7, 10,10a,12-octahydro-1,8,10a,11-tetra hydroxy-10,12-dioxo-2-naphthacenyl]-α-ethyl-1H-imidazole-1-acetamide dihydrochloride

[Compound of Formula I where R=H; X=Cl; W=1-H-Imidazol-1-yl; R^3=H; R^4=Et]

[0080] Substantially following the method, described in detail herein above in Example 36, the compounds of the invention listed in Examples 67 - 68 are prepared from [4S-(4α,12aα)]-9-[(bromopropionyl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11.12a-octahydro-3,10,12.12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide.

Example 67

[4S-(4α,12aα)]-8-Chloro-9-[[2-(diethylamino)-1-oxopropyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene carboxamide

[Compound of Formula I where R=H; X=Cl; W=NEt_2; R^3=H; R^4=H]

Example 68

[7S-(7α,10aα)]-1-[2-[[9-(Aminocarbonyl)-3-chloro-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-1-methyl-2-oxoethyl] proline methyl ester

[Compound of Formula I where R=H; X=Cl; W=-2-methoxycarbonyl-pyrrolidin-1-yl; R^3=CH_3; R^4=H]

Example 69

[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-7-(dimethyl amino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetra hydroxy-10,12-dioxo-2-naphthacenyl]-α-(4-hydroxyphenyl)-6-methyl-2,6-diazabicyclo-[2.1.1]heptane-2-acetamide

[Compound of Formula I where R=H; X=Cl; W=6-methyl-2,6-diazabicyclo[2.1.1]heptan-2-yl; R^3=H; R^4=hydroxyphenyl]

[0081] The title compound is prepared by the procedure of Example 36 using [4S-(4α,12aα)]-9-[[(4-Hydroxyphenyl)-α-bromoacetyl]amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a, 6,11,12a-octahydro-3,10,-12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide and 6-methyl-2,6-diazabicyclo [2.1.1]heptane.

Example 70

[4S-(4α,12aα)]-8-Chloro-4-(dimethylamino)-9-[[(dimethyl amino)(2-fluorophenyl)acetyl]amino]-1,4,4a,5,5a,6,11,12a octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

[Compound of Formula I where R=H; X=Cl; W=NMe_2; R^3=2-fluorophenyl; R^4=H]

[0082] The title compound is prepared by the procedure of Example 36 using [4S-(4α,12aα)]-9-[[(2-fluorophenyl)-α-bromoacetyl]amino]-8-chloro-4-(di-methylamino)-1,4,4a,5,5a, 6,11,12a-octahydro-3,10,12,-12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide and dimethylamine.

Example 71

[4S-(4α,12aα)]-8-Chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[1-(4-methoxy-1-piperazinyl)-4-pentenoyl]amino]-1,11-dioxo-2-naphthacene carboxamide

[Compound of Formula I where R=H; X=Cl; W=4-methoxypiperazin-1-yl; R^3=$CH_2CH_2CH{=}CH_2$; R^4=H]

[0083] The title compound is prepared by the procedure of Example 36 using [4S-(4α,12aα)]-9-[(2-bromo-4-pentenoyl) amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3, 10,12,12a-tetra-hydroxy-1,11-dioxo-2-naphthacenecarboxamide and 4-methoxypiperazine.

Example 72

[4S-(4α,12aα)]-8-Chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[1-oxo -4-phenyl-2-[(phenylmethoxy)amino]butyl]amino]-2-naphthacene carboxamide

[Compound of Formula I where R=H; X=Cl; W=-$NHCH_2Ph$; R^3=2-phenylethyl; R^4=H]

[0084] The title compound is prepared by the procedure of Example 36 using [4S-(4α,12aα)]-9-[(α-bromophenyl butyryl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a, 6,11,12a-octahydro-3,10,12,12a-tetra-hydroxy-1,11-dioxo-2-naphthacenecarboxamide and benzyloxyamine.

Example 73

[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-7-(dimethyl amino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-α-4-pyridyl-5-aza bicyclo[2.1.1]hexan-5-acetamide

[Compound of Formula I where R=H; X=Cl; W=azabicyclo[2.1.1]hex-1-yl; R^3=4-pyridyl; R^4=H]

[0085] The title compound is prepared by the procedure of Example 36 using [4S-(4α,12aα)]-9-[[(4-pyridyl)-α-bromo acetyl]amino]-8-chloro-4-(dimethyl-amino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide and 5-azabicyclo[2.1.1]hexane.

[0086] Substantially, following the method, described in detail herein above in Example 36, the compounds of the invention listed in Examples 74 - 75 are prepared from [4S-(4α,12aα)]-9-[(bromoacetyl)amino]-4-(di-methylamino)-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide.

Example 74

[4S-(4α,12aα)]-4-(Dimethylamino)-9-[[(dimethylamino)acetyl] amino]-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

[Compound of Formula I where R=H; X=F; W=NMe_2; R^3=H; R^4=H]

Example 75

[4S-(4α,12aα)1-4-(Dimethyamino)-8-fluoro-1,4,4a,5,5a,6, 11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(propyl amino)acetyl]amino]-2-naphthacenecarboxamide

[Compound of Formula I where R=H; X=F; W=NHPr; R^3=H; R^4=H]

Example 76

[4S-(4α,12aα)]-4-(Dimethylamino)-9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-8-[[(trifluoromethyl)sulfonyl] oxy]-2naphthacene carboxamide

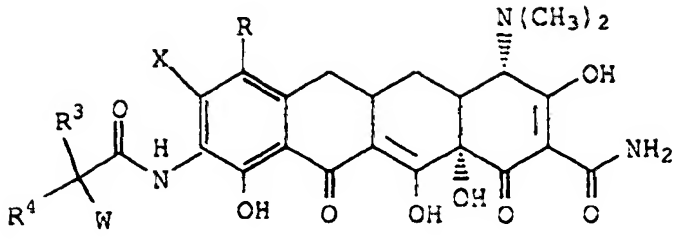
[Compound of Formula I where R=H; X=OSO_2CF_3; W=NMe_2; R^3=H; R^4=H]

[0087] The title compound is prepared by the procedure of Example 36 using [4S-(4α,12aα)]-9-[(bromoacetyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12, 12a-tetrahydroxy-1,11-dioxo-8-[[(trifluoromethyl)sulfonyl] oxy]-2-naphthacenecarboxamide and dimethylamine.

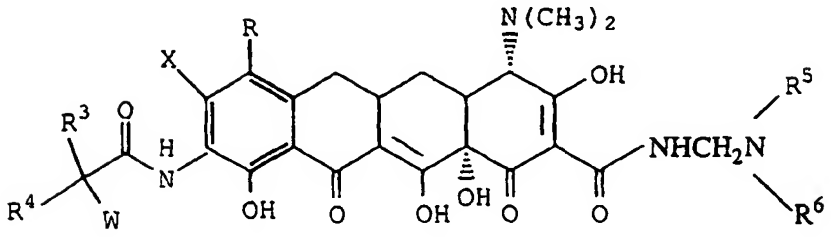
MASS SPECTRAL DATA	
Example #	MS (FAB):m/z
59	592 (M + H)
60	535 (M + H)
61	575 (M + H)
63	589 (M + H)

Claims

1. A compound of the formula :



I



II

wherein:

X is selected from trifluoromethanesulfonyloxy, bromine, chlorine, fluorine and iodine;

R is selected from

(i) hydrogen, bromine, chlorine, fluorine and iodine; and
(ii)-NR^1R^2 providing that when R – -NR^1R^2 and

(a) R^1 =hydrogen, then R^2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl; or
(b) R^1 = methyl or ethyl, then R^2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl; or
(c) R^1 = n-propyl, then R^2 = n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl; or
(d) R^1 = 1-methylethyl, then R^2 = n-butyl, 1-methylpropyl or 2-methylpropyl; or
(e) R^1 – n-butyl, then R^2 – n-butyl, 1-methylpropyl or 2-methylpropyl; or
(f) R^1 – 1-methylpropyl, then R^2 – 2-methylpropyl;

R^3 is selected from

hydrogen;
straight or branched (C_1-C_8)alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and octyl;
α-mercapto(C_1-C_4)alkyl group selected from mercaptomethyl, α-mercaptoethyl, α-mercapto-1-methylethyl, α-mercaptopropyl and α-mercaptobutyl;
α-hydroxy(C_1-C_4)alkyl group selected from hydroxymethyl, α-hydroxyethyl, α-hydroxy-1-methylethyl, α-hydroxypropyl and α-hydroxybutyl;
carboxyl(C_1-C_8)alkyl group;
(C_6-C_{10})aryl group selected from phenyl, α-naphthyl and β-naphthyl;

substituted(C_6-C_{10})aryl group (substitution selected from hydroxy, halogen, (C_1-C_4)alkoxy, trihalo-(C_1-C_3) alkyl, nitro, amino, cyano, (C_1-C_4)alkoxycarbonyl, (C_1-C_3)alkylamino and carboxy);
(C_7-C_9)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenylpropyl;
substituted(C_7-C_9)aralkyl group [substitution selected from halo, (C_1-C_4)alkyl, nitro, hydroxy, amino, mono- or disubstituted (C_1-C_4)alkylamino, (C_1-C_4)alkoxy, (C_1-C_4)alkylsulfonyl, cyano and carboxy];

R^4 is selected from hydrogen and (C_1-C_6)alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl;

when R^3 does not equal R^4 the stereochemistry of the asymmetric carbon (i.e., the carbon bearing the W substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D);

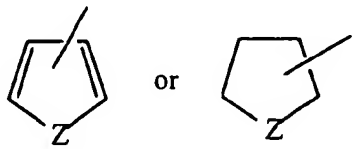
W is selected from

amino;
hydroxylamino;
(C_1-C_{12}) straight or branched alkyl monosubstituted amino group substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-di-methylpropyl, 2,2-dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethyl-butyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl-butyl, 1-methyl-1-ethylpropyl, heptyl, octyl, nonyl, decyl, undecyl and dodecyl and the diastereomers and enantiomers of said branched alkyl monosubstituted amino group;
(C_3-C_8)cycloalkyl monosubstituted amino group substitution selected from cyclopropyl, trans-1,2-dimethylcyclopropyl, cis-1,2-dimethylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicycle[2.2.1]hept-2-yl, and bicyclo[2.2.2]oct-2-yl and the diastereomers and enantiomers of said (C_3-C_8) cycloalkyl monosubstituted amino;
[(C_4-C_{10})cycloalkyl]alkyl monosubstituted amino group substitution selected from (cyclopropyl)methyl, (cyclopropyl)ethyl, (cyclobutyl)methyl, (trans-2-methylcyclopropyl)methyl, and (cis-2-methylcyclobutyl) methyl;
(C_3-C_{10})alkenyl monosubstituted amino group substitution selected from allyl, 3-butenyl, 2-butenyl (cis or trans), 2-pentenyl, 4-octenyl, 2,3-dimethyl-2-butenyl, 3-methyl-2-butenyl, 2-cyclopentenyl and 2-cyclohexenyl;
(C_6-C_{10})aryl monosubstituted amino group substitution selected from phenyl and naphthyl; (C_7-C_{10})aralkylamino group substitution selected from benzyl, 2-phenylethyl, lphenylethyl, 2-(naphthyl)methyl, 1-(naphthyl)methyl and phenylpropyl;
substituted (C_6-C_{10})aryl monosubstituted amino group [substitution selected from (C_1-C_5)acyl, (C_1-C_5) acylamino, (C_1-C_4)alkyl, mono or disubstituted (C_1-C_8)alkylamino, (C_1-C_4)alkoxy, (C_1-C_4)alkoxycarbonyl, (C_1-C_4)alkylsulfonyl, amino, carboxy, cyano, halogen, hydroxy, nitro and trihalo(C_1-C_3)alkyl];
straight or branched symmetrical disubstituted (C_2-C_{14})alkylamino group substitution selected from dimethyl, diethyl, diisopropyl, di-n-propyl, dibutyl and diisobutyl;
symmetrical disubstituted (C_3-C_{14})-cycloalkylamino group substitution selected from dicyclopropyl, dicyclobutyl, dicyclopentyl, dicyclohexyl and dicycloheptyl;
straight or branched unsymmetrical disubstituted (C_3-C_{14})alkylamino group wherein the total number of carbons in the substitution is not more than 14;
unsymmetrical disubstituted (C_4-C_{14})cycloalkylamino group wherein the total number of carbons in the substitution is not more than 14;
(C_2-C_8)azacycloalkyl and substituted (C_2-C_8)azacycloalkyl group substitution selected from aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, 4-methylpiperidinyl, 2-methylpyrrolidinyl, cis-3,4-dimethylpyrrolidinyl, trans-3,4-dimethylpyrrolidinyl, 2-azabicyclo[2.1.1]-hex-2-yl, 5-azabicyclo[2.1.1]hex-5-yl, 2-azabicyclo [2.2.1]hept-2-yl, 7-azabicyclo[2.2.1]hept-7-yl, 2-azabicyclo[2.2.2]oct-2-yl and the diastereomers and enantiomers of said (C_2-C_8)azacycloalkyl and substituted (C_2-C_8)azacycloalkyl group;
1-azaoxacycloalkyl selected from morpholinyl and 1-aza-5-oxocycloheptane;
substituted 1-azaoxacycloalkyl group substitution selected from 2-(C_1-C_3)alkylmorpholinyl, 3-(C_1-C_3) alkylisoxazolidinyl, tetrahydrooxazinyl and 3,4-dihydrooxazinyl;
[1,n]-diazacycloalkyl and substituted [1,n]-diazacyclo-alkyl group selected from piperazinyl, 2-(C_1-C_3) alkyl-piperazinyl, 4-(C_1-C_3)alkylpiperazinyl, 2,4-dimethylpiperazinyl, 4-(C_1-C_4)alkoxypiperazinyl, 4-(C_6-C_{10})-aryloxypiperazinyl, 4-hydroxypiperazinyl, 2,5-diazabicyclo[2.2.1]hept-2-yl, 2,5-diaza-5-methylbicyclo-[2.2.1]hept-2-yl, 2,3-diaza-3-methylbicyclo[2.2.2]oct-2-yl, 2,5-diaza-5,7-dimethylbicyclo[2.2.2]oct-2-yl

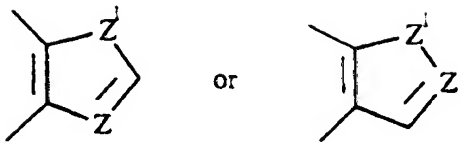
and the diastereomers or enantiomers of said [1,n]-diaza-cycloalkyl and substituted [1,n]-diazacycloalkyl group;
1-azathiacycloalkyl and substituted 1-azathiacycloalkyl group selected from thiomorpholinyl, 2-(C_1-C_3)-alkylthiomorpholinyl and 3-(C_3-C_6)cycloalkylthiomorpholinyl;
N-azolyl and substituted N-azolyl group selected from 1-imidazolyl, 2-(C_1-C_3)alkyl-1-imidazolyl, 3-(C_1-C_3) alkyl-1-imidazolyl, 1-pyrrolyl, 1-pyrazolyl, 2-(C_1-C_3)alkyl-1-pyrrolyl, 3-(C_1-C_3)alkyl-1-pyrazolyl, indolyl, 1-(1,2,3-triazolyl), 4-(C_1-C_3)alkyl-1-(1,2,3-triazolyl), 5-(C_1-C_3)alkyl-1-(1,2,3-triazolyl), 4-(1,2,4-triazolyl, 1-tetrazolyl, 2-tetrazolyl and benzimidazolyl;
(heterocycle)amino group selected from 2- or 3-furanylamino, 2- or 3-thienylamino, 2-, 3- or 4-pyridylamino, 2- or 5-pyridazinylamino, 2-pyrazinylamino, 2-(imidazolyl)amino, (benzimidazolyl)amino, and (benzothiazolyl)amino and substituted (heterocycle)amino group as defined above with substitution selected from straight or branched (C_1-C_6)alkyl;
(heterocycle)methylamino group selected from 2-or 3-furylmethylamino, 2- or 3-thienylmethylamino, 2-, 3- or 4-pyridylmethylamino, 2- or 5-pyridazinylmethyl-amino, 2-pyrazinylmethylamino, 2-(imidazolyl)methylamino, (benzimidazolyl)methylamino, and (benzothiazolyl)methylamino and substituted (heterocycle) methylamino as defined above with substitution selected from straight or branched (C_1-C_6)alkyl;
carboxy(C_2-C_4)alkylamino group selected from aminoacetic acid, α-aminopropionic acid, β-aminopropionic acid, α-butyric acid, and β-aminobutyric acid and the enantiomers of said carboxy(C_2-C_4)alkylamino group;
(C_1-C_4)alkoxycarbonylamino group substitution selected from methoxycarbonyl, ethoxycarbonyl, allyloxycarbonyl, propoxycarbonyl, isoproproxycarbonyl, 1,1-dimethylethoxycarbonyl, n-butoxycarbonyl, and 2-methylpropoxycarbonyl;
(C_1-C_4)alkoxyamino group substitution selected from methoxy, ethoxy, n-propoxy, 1-methylethoxy, n-butoxy, 2-methylpropoxy, and 1,1-dimethylethoxy;
(C_3-C_8)cycloalkoxyamino group selected from cyclopropoxy, trans-1,2-dimethylcyclopropoxy, cis-1,2-dimethylcyclopropoxy, cyclobutoxy, cyclopentoxy, cyclohexoxy, cycloheptoxy, cyclooctoxy, bicyclo-[2.2.1]hept-2-yloxy, bicyclo[2.2.2]oct-2-yloxy and the diastereomers and enantiomers of said (C_3-C_8)cycloalkoxyamino group;
and
(C_6-C_{10})aryloxyamino group selected from phenoxyamino, 1-naphthyloxyamino and 2-naphthyloxyamino;
(C_7-C_{11})arylalkoxyamino group substitution selected from benzyloxy, 2-phenylethoxy, 1-phenylethoxy, 2-(naphthyl)methoxy, 1-(naphthyl)methoxy and phenylpropoxy;

R^5 and R^6 are independently selected from

(i) hydrogen, with the proviso that R^5 and R^6 cannot both be hydrogen;
(ii) straight or branched (C_1-C_3)-alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl;
(iii) (C_6-C_{10})aryl group selected from phenyl, α-naphthyl or β-naphthyl;
(iv) (C_7-C_9)aralkyl group such as benzyl, 1-phenylethyl, 2-phenyl or phenylpropyl;
(v) a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

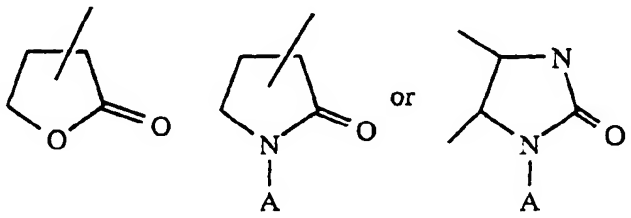


Z–N, O, S or Se such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl,
(vi) a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:



Z or Z^1 = N, O, S or Se such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-imidazo[4,5-b]pyridyl or pyridylimidazolyl,

(vii) a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



(wherein A is selected from hydrogen; straight or branched (C_1-C_4)alkyl; C_6-aryl; substituted C_6-aryl (substitution selected from halo, (C_1-C_4)alkoxy, trihalo(C_1-C_3)alkyl, nitro, amino, cyano, (C_1-C_4)alkoxycarbonyl, (C_1-C_3)alkylamino or carboxy); (C_7-C_9)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl);

such as γ-butyrolactam, γ-butyrolactone, imidazolidinone or N-aminoimidazolidinone,

(viii) or a six membered aromatic ring with one to three N heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, sym-triazinyl, unsym-triazinyl, pyrimidinyl or (C_1-C_3)alkylthiopyridazinyl,

(ix) or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxo-1-piperazinyl, 2-dioxomorpholinyl and 2-dioxothiomorpholinyl;

(x) -$(CH_2)_n$COOR^7 where n–0-4 and R^7 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl;

or

(xi) (C_6-C_{10})aryl group selected from phenyl, α-naphthyl or β-naphthyl;

or **R^5 and R^6** taken together are -$(CH_2)_2B(CH_2)_2$-,

wherein B is selected from $(CH_2)_n$ and n–0-1, -NH, -N(C_1-C_3)alkyl [straight or branched], -N(C_1-C_4)alkoxy, oxygen, sulfur or substituted congeners selected from (L or D)proline, ethyl(L or D)prolinate;

and the pharmacologically acceptable organic and inorganic salts or metal complexes.

2. The compound according to Claim 1, wherein:

X is chlorine, fluorine or trifluoromethanesulfonyloxy;

R is selected from hydrogen, chlorine, iodine or -NR^1R^2 wherein **R^1** and **R^2** are independently methyl or ethyl,

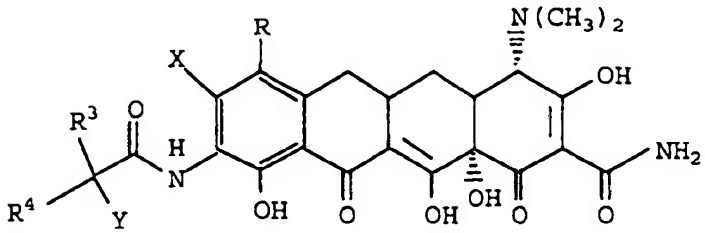
R^3 and **R^4** are independently hydrogen, methyl and ethyl, and when R^3 does not equal R^4 the stereochemistry of the asymmetric carbon (i.e., the carbon bearing the W substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D);

W is selected from amino; methylamino, ethylamino, n-propylamino, 1-methylethylamino, n-butylamino, 1-methylpropylamino.cyclopropylamino, cyclobutylamino, pyrrolidinyl, piperidinyl, 4-methylpiperidinyl, mor-

pholinyl, piperazinyl, 4-(C_1-C_3)alkylpiperazinyl,1-imidazolyl, 2-(C_1-C_3)alkyl-1-imidazolyl, 3-(C_1-C_3)alkyl-1-imidazolyl, 2-, 3-or 4-pyridylmethylamino, carboxy(C_2-C_4)alkylamino groups selected from aminoacetic acid, α-aminopropionic acid, β-aminopropionic acid α-butyric acid and β-aminobutyric acid and the enantiomers of said carboxy(C_2-C_4)alkylamino group:

R^5 and R^6 are independently selected from hydrogen, methyl, ethyl, n-propyl and 1-methylethyl; with the proviso that R^5 and R^6 cannot both be hydrogen:
or R^5 and R^6 taken together are -$(CH_2)_2B(CH_2)_2$-, wherein B is selected from $(CH_2)_n$ and n=0-1, -NH, -N(C_1-C_3)alkyl [straight or branched], -N(C_1-C_4)alkoxy, oxygen, sulfur or substituted congeners selected from (L or D)proline, ethyl(L or D)prolinate; and the pharmacologically acceptable organic and inorganic salts or metal complexes.

3. A compound of the formula (III):



III

wherein:

Y is selected from bromine, chlorine, fluorine and iodine; and
R, X, R^3 and R^4 are as defined in Claim 1.

4. The compound according to Claim 3, wherein:

Y is selected from bromine, chlorine, fluorine and iodine;
X is or trifluoromethanesulfonyloxy, chlorine or fluorine;
R is selected from hydrogen; chlorine, iodine or -NR^1R^2 where R^1 and R^2 are each independently methyl or ethyl;
R^3 is selected from hydrogen, methyl and ethyl;
R^4 is selected from hydrogen, methyl and ethyl;
when R^3 does not equal R^4 the stereochemistry of the asymmetric carbon (i.e., the carbon bearing the W substituent) may be either the racemate (DL) or the individual enantiomers (L or D); and the pharmacologically acceptable organic and inorganic salts or metal complexes.

5. The compound according to Claims 1-3 wherein said salts or metal complexes comprise: hydrochloric, hydrobromic, hydroiodic, phosphoric, nitric, sulfate, acetate, benzoate, citrate, cysteine or other amino acid, fumarate, glycolate, maleate, succinate, tartrate, alkylsulfonate, arylsulfonate, aluminum, calcium, iron, magnesium or manganese.

6. A compound according to Claim 1, which is one of the following:

[4S-(4α,12aα)]]-8-Chloro-4- (dimethylamino) -9-[[(dimethyl amino)acetyl]amino]-1,4,4a,5,5a,-6,11,12a-octahydro-3,10, 12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide disulfate
[Compound of formula I where R=H; X=Cl; R^3=H; R^4=H; W=NMe_2; disulphate salt]

[4S-(4α,12aα)]-8-Chloro-4-(dimethylamino)-9-[[(dimethyl amino)acetyl]amino]-1,4,4a,5,5a,-6 11,12a-octahy-

dro-3,10, 12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
[Compound of formula I where R=H; X=Cl; W=NMe_2; R^3=H; R^4=H]

[4S-(4α,12aα)]-8-Chloro-4,7-(dimethylamino)-9-[[(dimethyl amino)acetyl]amino]-1,4,4a,5,5a,6,11,-12a-octahydro-3,10,12, 12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
[Compound of formula I where R=NMe_2; X=Cl; W=NMe_2; R^3=H; R^4=H]

[4S-(4α,12aα)]-9-[[(Butylamino)acetyl]amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12, 12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
[Compound of formula I where R=NMe_2; X=Cl; W=NHBu; R^3=H; R^4=H]

[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis (dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1H-pyrrole-1-acetamide
[Compound of formula I where R=NMe_2; X=Cl; W=1H-pyrrol-1-yl; R^3=H; R^4=H]

[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis (dimethyl amino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1H-pyrazole-1-acetamide
[Compound of formula I where R=NMe_2; X=Cl; W=1H-pyrazol-1-yl; R^3=H; R^4=H]

[4S-(4α,12aα)]-8-Chloro-4,7-bis(dimethylamino)-9-[[[1,1-dimethylethyl)amino]acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene carboxamide
[Compound of formula I where R=NMe_2; X=Cl; W=NHTBu; R^3=H; R^4=H]

[4S-(4α,12aα)]-8-Chloro-9-[[(cyclopropylamino)acetyl]amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
[Compound of formula I where R=NMe_2; X=Cl; W=cyclopropylamino; R^3=H; R^4=H]

[4S-(4α,12aα)]-8-Chloro-9-[[[(cyclobutyloxy)amino]acetyl] amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,-11,12a-octahydro -3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
[Compound of formula I where R=NMe_2; X=Cl; W=cyclobutyloxyamino; R^3=H; R^4=H]

[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis(dimethyl amino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1-pyrrolidineacetamide
[Compound of formula I where R=NMe_2; X=Cl; W=pyrrolidin-1-yl; R^3=H; R^4=H]

[4S-(4α,12aα)]-8-Chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6, 11,12a-octahydro-3,10,12,12a-tetrahydroxy-1, 11-dioxo-9-[[[(propylamino)]acetyl]amino]-2-naphthacenecarboxamide
[Compound of formula I where R=NMe_2; X=Cl; W=NHPr; R^3=H; R^4=H]

[4S-(4α,12aα)]-8-Chloro-4,7-bis(dimethylamino)-1,4,-4a,5,5a,6, 11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[1-oxo-2-(propylamino)propyl]amino]-2-naphthacenecarboxamide
[Compound of formula I where R=NMe_2; X=Cl; W=NHPr; R^3=H; R^4=CH_3]

[4S-(4α,12aα)]-4,7-Bis(Dimethylamino)-9-[[(dimethyl- amino) acetyl]amino]-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
[Compound of formula I where R=NMe_2; X=F; W=NMe_2; R^3=H; R^4=H]

[4S-(4α,12aα)]-9-[[(Butylamino)acetyl]amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxonaphthacenecarboxamide dihydrochloride **[Compound of formula I where R=H; X=Cl; W=NHBu; R^3=H; R^4=H;hydrochloride salt]**

[4S-(4a,12aa)]-8-Chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(propyl amino)acetyl]amino]-2-naphthacenecarboxamide dihydrochloride
[Compound of formula I where R=H; X=Cl; W=NHPr; R^3=H; R^4=H;hydrochloride salt]

[4S-(4α,12aα)]-8-Chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(pentyl amino)acetyl]amino]-2-naphthacenecarboxamide dihydrochloride
[Compound of formula I where R=H; X=Cl; W=phenylamino; R^3=H; R^4=H;hydrochloride salt]

[4S-(4α,12aα)]-8-Chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(methyl amino)acetyl]amino]-2-naphthacenecarboxamide dihydrochloride
[Compound of formula I where R=H; X=Cl; W=NHMe; R^3=H; R^4=H; hydrochloride salt]

[4S-(4α,12aα)]-8-Chloro-9-[[(cyclopropylmethylamino)-acetyl] amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10, 12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride
[Compound of formula I where R=H; X=Cl; W=cyclopropylmethylamino; R^3=H; R^4=H;hydrochloride salt]

[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-7-(dimethyl amino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetra hydroxy-10,12-dioxo-2-naphthacenyl]-1-pyrrolidineacetamide dihydrochloride
[Compound of formula I where R=H; X=Cl; W=pyrrolidin-1-yl; R^3=H; R^4=H;hydrochloride salt]

[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-7-(dimethyl amino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetra hydroxy-10,12-dioxo-2-naphthacenyl]-1-piperidineacetamide dihydrochloride
[Compound of formula I where R=H; X=Cl; W=piperidin-1-yl;R^3=H; R^4=H;hydrochloride salt]

7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-7-(dimethylamino)

-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-5-azabicyclo[2.1.1]hexane-5-acetamide dihydrochloride
[Compound of formula I where R=H; X=Cl; W=azabicyclo[2.1.1]hex-5-yl; R^3=H; R^4=H;hydrochloride salt]

[4S-(4α,12aα)]-8-Chloro-9-[[(cyclobutylamino)acetyl] -amino] -4-(dimethylamino)-1,4,4a,5,5a,6,11,12a- octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride
[Compound of formula I where R=H; X=Cl; W=cyclobutylamino; R^3=H; R^4=H;hydrochloride salt]

[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetra hydroxy-10,12-dioxo-2-naphthacenyl]-α-ethyl-1H-imidazole-1- acetamide dihydrochloride
[Compound of formula I where R=H; X=Cl; W=1-H-imidazol-1-yl; R^3=H; R^4=Et;hydrochloride salt]

[4S-(4α,12aα)]-8-Chloro-9-[[2-(diethylamino)-1-oxo-propyl] amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10, 12,12a-tetrahydroxy-1, 11-dioxo-2-naphthacenecarboxamide
[Compound of formula I where R=H; X=Cl; W=NEt_2; R^3=H; R^4=H]

[4S-(4α,12aα)]-8-Chloro-4-(dimethylamino)-9-[[(di-methyl amino)(2-fluorophenyl)acetyl]amino]-1,4,4a,5,-5a,6,11,12a-octahydro-3, 10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene carboxamide
[Compound of formula I where R=H; X=Cl; W=NMe_2; R^3=2-fluorophenyl; R^4=H]

[4S-(4α,12aα)]-8-Chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-1,-11-dioxo-9-[[1-oxo-4-phenyl-2-[(phenylmethoxy)amino]butyl]amino]-2-naphthacene carboxamide
[Compound of formula I where R=H; X=Cl; W=-$NHCH_2Ph$; R^3=2-phenylethyl; R^4=H]

[4S-(4α,12aα)]-4-(Dimethylamino)-9-[[(dimethylamino)-acetyl]amino]-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
[Compound of formula I where R=H; X=F; W=NMe_2; R^3=H; R^4=H]

[4S-(4α,12aα)]-4-(Dimethylamino)-8-fluoro-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(propyl amino)acetyl]amino]-2-naphthacenecarboxamide
[Compound of formula I where R=H; X=F; W=NHPr; R^3=H; R^4=H]

[4S-(4α,12aα)]-4-(Dimethylamino)-9-[[(dimethylamino)-acetyl] amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra hydroxy-1,11-dioxo-8-[[(trifluoro-methyl)sulfonyl]oxy]-2-naphthacenecarboxamide
[Compound of formula I where R=H; X=O-SO_2-CF_3; W=NMe_2; R^3=H; R^4=H]

7. A compound according to Claim 3, which is one of the following:

[4S-(4α,12aα)]-9-(Chloroacetyl)amino]-8-chloro-4,7-bis (dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3, 10,12, 12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
[Compound of formula III where R=NMe_2; X=Cl; R^3=H; R^4=H; Y=Cl]

[4S-(4α,12aα)]-9-[(Bromoacetyl)amino]-8-chloro-4,7-bis (dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3, 10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
[Compound of formula III where R=NMe_2; X=Cl; R^3=H; R^4=H; Y=Br]

[4S-(4α,12aα)]-9-[(α-Bromopropionyl)amino]-8-chloro-4,7-bis (dimethylamino)-1,4,4a,5,5a,-6,11,12a-octahydro-3,10,12, 12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
[Compound of formula III where R=NMe_2; X=Cl; R^3=H; R^4=Me; Y=Br]

[4S-(4α,12aα)]-9-[(α-Bromophenylacetyl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12, 12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
[Compound of formula III where R=NMe_2; X=Cl; R^4=H; R^3=Ph; Y=Br]

[4S-(4α,12aα)]-9-[(α-Bromo-2,2-dimethylbutyryl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
[Compound of formula III where R=NMe_2; X=Cl; R^3=Isopropyl; R^4=H; Y=Br]

[4S-(4α,12aα)]-9-[(α-Bromo-(2,4-difluorophenyl)acetyl)-amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,-5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
[Compound of formula III where R=NMe_2; X=Cl; R^3=2,4-difluorophenyl; R^4=H; Y=Br]

[4S-(4α,12aα)]-9-[(Bromoacetyl)amino]-4,7-bis-(dimethyl amino)-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
[Compound of formula III where R=NMe_2; X=F; R^3=H; R^4=H; Y=Br]

[4S-(4α,12aα)]-9-[(Bromoacetyl)amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra hydroxy-1,11-dioxo-8-[[(trifluoromethyl)-sulfonyl]oxy]-2-naphthacenecarboxamide
[Compound of formula III where R=NMe_2; X=OSO_2CF_3; R^3=H; R^4=H; Y=Br; hydrochloride salt]

[4S-(4α,12aα)]-9-[(Chloroacetyl)amino]-8-chloro-4-(dimethyl amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10, 12,12a-tetra hydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride
[Compound of formula III where R=H; X=Cl; R^3=H; R^4=H; Y=Cl; hydrochloride salt]

[4S-(4α,12aα)]-9-[(Bromoacetyl)amino]-8-chloro-4-(dimethyl amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10, 12,12a-tetra hydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide
[Compound of formula III where R=H; X=Cl; R^3=H; R^4=H; Y=Br; hydrobromide salt]

[4S-(4α,12aα)]-9-[(2-Chloropropionyl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride
[Compound of formula III where R=H; X=Cl; R^3=H; R^4=Me; Y=Cl; hydrochloride salt]

[4S-(4α,12aα)]-9-[(2-Chlorobutyryl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3, 10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride
[Compound of formula III where R=H; X=Cl; R^3=H; R^4=Et; Y=Cl; hydrochloride salt]

4S-(4α,12aα)]-9-[[(4-Hydroxyphenyl)-α-chloroacetyl]-amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,-12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene carboxamide hydrochloride
[Compound of formula III where R=H; X=Cl; R^3=4-hydroxyphenyl; R^4=H; Y=Cl; hydrochloride salt]

[4S-(4α,12aα)]-9-[[(2-Fluorophenyl)-α-bromoacetyl]-amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,-12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene carboxamide hydrobromide
[Compound of formula III where R=H; X=Cl; R^3=2-fluoro phenyl; R^4=H; Y=F;hydrobromide salt]

[4S-(4α,12aα)]-9-[(α-Bromo4-phenylbutyryl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide

[Compound of formula III where R=H; X=Cl; R^3=2-phenylethyl; R^4=H; Y=Br; hydrobromide salt]

[4S-(4α,12aα)]-9-[(Bromoacetyl)amino]-4-(dimethylamino)-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra hydroxy-1,11-dioxo-2-naphthacenecarboxamide
[Compound of formula III where R=H; X=F; R^3=H; R^4=H; Y=Br]

[4S-(4α,12aα)]-9-[(Bromoacetyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-8-[[(trifluoromethyl)sulfonyl]oxy]-2-naphthacene carboxamide
[Compound of formula III where R=H; X= OSO_2CF_3; R^3=H; R^4=H; Y=Br]

8. A compound selected from:

[4S-(4α,12aα)]-8-Chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a, 6,11,12a-octahydro-3,10,12,12a-tetra-hydroxy-9-[[[(3-methyl cyclobutyl)amino]acetyl]amino]-1,11-dioxo-2-naphthacene carboxamide
[Compound of formula I where R=NMe_2; X=Cl; W=3-methylcyclobutylamino; R^3=H; R^4=H]

[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis-(dimethyl amino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,9,10a,11-tetra hydroxy-10,12-dioxo-2-naphthacenyl]-(3-methyl-1-pyrrolidine) acetamide
[Compound of formula I where R=NMe_2; X=Cl; W=3-methyl-pyrrolidin-1-yl; R^3=H; R^4=H]

[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-α-cyclobutyl tetrahydro-2H-1,2-isoxazine-2-acetamide
[Compound of formula I where R=NMe_2; X=Cl; W=tetrahydro-2H-1,2-isoxazin-2-yl; R^3=H; R^4=cyclobutyl]

[4S-(4α,12aα)]-8-Chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a, 6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[phenyl[(phenylmethyl)amino]acetyl]amino]-2-naphthacene carboxamide
[Compound of formula I where R=NMe_2; X=Cl; W=phenyl(phenylmethyl)amino; R^3=H; R^4=H]

[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis(dimethyl amino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-α-cyclopropyl-a-methyl-1-azetidine acetamide
[Compound of formula I where R=NMe_2; X=Cl; W=azetidin-1-yl; R^4=CH_3; R^3=cyclopropyl]

[7S-(7α,10aα)]-N-[9- (Aminocarbonyl)-3-chloro-4,7-bis-(dimethyl amino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-α--(1,1dimethylethyl)-(3-methyl-4-morpholine)acetamide
[Compound of formula I where R=NMe_2; X=Cl; W=3-methyl-morpholin-4-yl; R^3=tBu; R^4=H]

[4S-(4α,12aα)]-8-Chloro-9-[[(2,4-difluorophenyl)[(2-phenyl ethyl)amino]acetyl]amino]-4,7-bis(dimethyl-amino)-1,4,4a,5,5a, 6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
[Compound of formula I where R=NMe_2; X=Cl; W=(2,4-difluoro phenyl)(2-phenylethyl)amino; R^3=H; R^4=H]

[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis(dimethyl amino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-α-(methoxyamino)-α-methyl-2-furan acetamide
[Compound of formula I where R=NMe_2; X=Cl; W=NHOMe; R^3=furan-2-yl; R^4=CH_3]

[7S-(7α,10aα)]-4-[[9-(Aminocarbonyl)-3-chloro-4,7- bis (dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-amino-3-[(1,1-dimethylethyl)amino]-4-oxobutanoic acid methyl ester
[Compound of formula I where R=NMe_2; X=Cl; W=-NHTBu; R^3=CH_2COOMe; R^4=H]

[7S-(7α,10aα)]-4-[[9-(Aminocarbonyl)-3-chloro-4,7- bis (dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-amino]-3-(dimethyl amino)-4-oxobutanoic acid methyl ester
[Compound of formula I where R=NMe_2; X=Cl; W=NMe_2; R^3=CH_2COOMe; R^4=H]

[7S-(7α,10aα)]-γ-[[9-(Aminocarbonyl)-3-chloro-4,7- bis (dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,

8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-amino]carbonyl]-1-pyrrolidinebutanoic acid methyl ester
[Compound of formula I where R=NMe_2; X=Cl; W=pyrrolidin-1-yl; $R^3=CH_2CH_2COOMe$; R^4=H]

[7S-(7α,10aα)]-1-[2-[[9-(Aminocarbonyl)-3-chloro-7-(dimethyl amino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetra hydroxy-10,12-dioxo-2-naphthacenyl]amino]-1-methyl-2-oxo ethyl] proline methyl ester
[Compound of formula I where R=H; X=Cl; W=-2-methoxycarbonyl-pyrrolidin-1-yl; $R^3=CH_3$; R^4=H]

[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-7-(dimethyl amino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetra hydroxy-10,12-dioxo-2-naphthacenyl]-α-(4-hydroxyphenyl)-6-methyl-2,6-diazabicyclo-[2.1.1]heptane-2-acetamide
[Compound of formula I where R=H; X=Cl; W=6-methyl-2,6-diazabicyclo [2.1.1]heptan-2-yl; R^3=hydroxyphenyl; R^4=H]

[4S-(4α,12aα)]-8-Chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[1-(4-methoxy-1-piperazinyl)-4-pentenoyl]amino]-1,11-dioxo-2-naphthacene carboxamide
[Compound of formula I where R=H; X=Cl; W=4-methoxypiperazin-1-yl; $R^3=CH_2CH_2CH=CH_2$; R^4=H]

[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chloro-7-(dimethyl amino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetra hydroxy-10,12-dioxo-2-naphthacenyl]-α-4-pyridyl-5-azabicyclo[2.1.1]hexan-5-acetamide
[Compound of formula I where R=H; X=Cl; W=azabicyclo[2.1.1]hex-1-yl; R^3=4-pyridyl; R^4=H]

9. A compound selected from:

[4S-(4α,12aα)]-9-[(α-Bromocyclobutylacetyl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene carboxamide
[Compound of formula III where R=NMe_2; X=Cl; R^4=H; R^3=cyclobutyl; Y=Br]

[4S-(4α,12aα)]-9-[(α-Bromo-α-cyclopropylpropionyl)-amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,-6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
[Compound of formula III where R=NMe_2; X=Cl; R^3=cyclopropyl; R^4=Me; Y=Br]

[4S-(4α,12aα)]-9-[(α-Bromo-(2-furyl)propionyl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5, 5a,6, 11, 12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
[Compound of formula III where R=NMe_2; X=Cl; R^3=furanylmethyl; R^4=H; Y=Br]

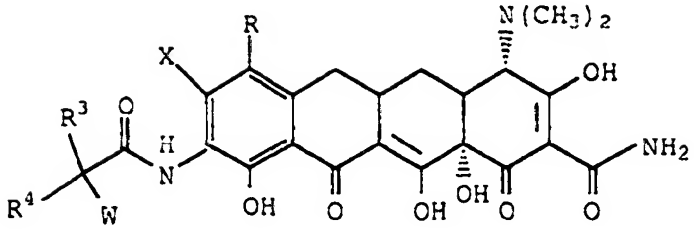
[4S-(4α,12aα)]-9-[(α-Bromo-(3-methoxycarbonyl-propionyl))amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
[Compound of formula III where R=NMe_2; X=Cl; R^3=methoxylcarbonylmethyl; R^4=H; Y=Br]

[4S-(4α,12aα)]-9-[(α-Bromo(4-methoxycarbonylbutyryl)) amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a, 6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
[Compound of formula III where R=NMe_2; X=Cl; R^3=methoxylcarbonylethyl; R^4=H; Y=Br]

[4S-(4α,12aα)]-9-[(2-Bromo-4-pentenoyl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide
[Compound of formula III where R=H; X=Cl; R^3=-$CH_2CH=CH_2$; R^4=H; Y=F;hydrobromide salt]

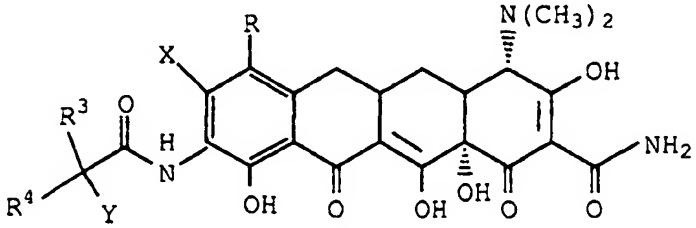
[4S-(4α,12aα)]-9-[((4-Pyridyl)-α-bromoacetyl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene carboxamide hydrobromide
[Compound of formula III where R=H; X=Cl; R^3=4-pyridyl; R^4=H; Y=Br; hydrobromide salt]

10. A method of producing a compound, or its organic and inorganic salts or metal complexes of the formula:



I

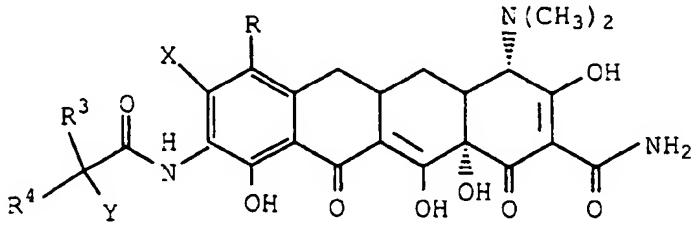
according to Claim 1, which comprises reacting a 9-[(haloacyl)amido]-7-(substituted)-8-(substituted)-6-demethyl-6-deoxytetracycline, or its organic and inorganic salt or metal complex, of the formula:



III

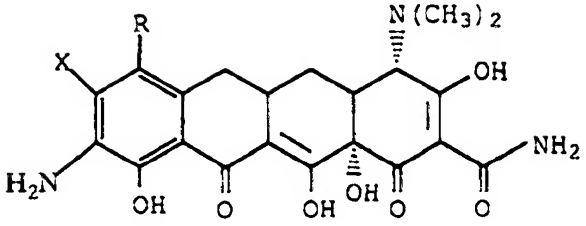
according to Claim 3, with a nucleophile of the formula WH, wherein W is as defined in Claim 1, in a polar protic or a polar-aprotic solvent and in an inert atmosphere.

11. A method of producing a compound, or its organic and inorganic salt or metal complex, of the formula:

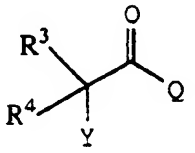


III

according to Claim 3, which comprises reacting a 9-amino-7-(substituted)-8-(substituted)-6-demethyl-6-deoxytetracycline, or its organic and inorganic salt or metal complex, of the formula:

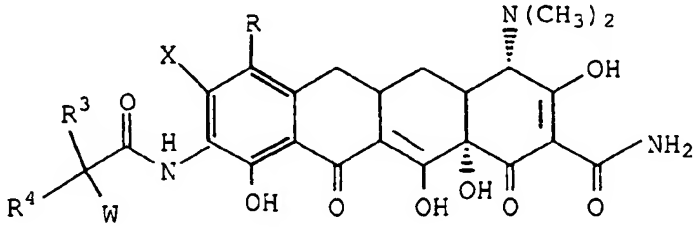


with a straight or branched haloacyl halide of the formula:



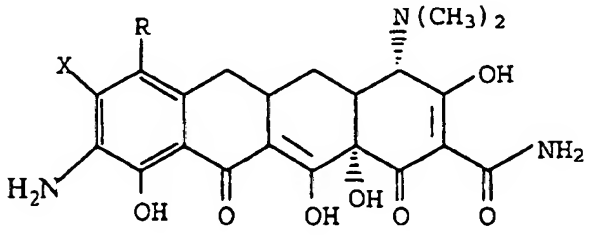
wherein Y, R^3 and R^4 are as defined in Claim 1 and Q is halogen selected from bromine, chlorine, iodine and fluorine, in an inert solvent, in a polar protic solvent and in the presence of a base.

12. A method of producing a compound, or its organic and inorganic salt or metal complex, of the formula:

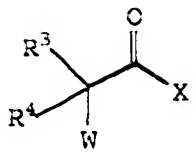


I

according to Claim 1, which comprises reacting a 9-amino-7-(substituted)-8-(substituted)-6-demethyl-6-deoxy-tetracycline, or its organic and inorganic salt or metal complex, of the formula:

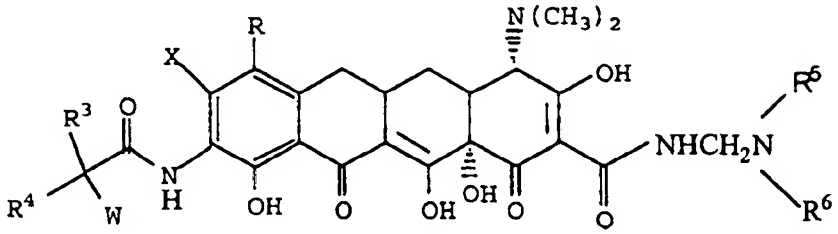


with a straight or branched acid chloride of the formula:



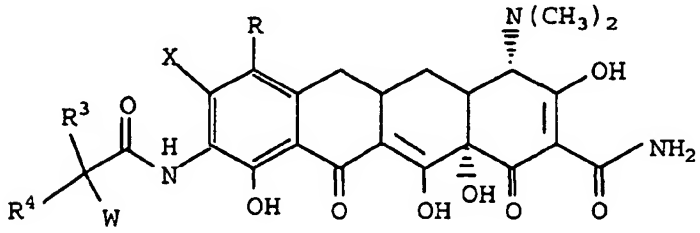
wherein R^3,R^4 and W are as defined in Claim 1 and X is halogen selected from bromine, chlorine, iodine and fluorine, in a suitable acid scavenger and suitable solvent.

13. A method of producing a compound of the formula:



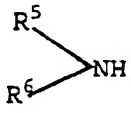
II

according to Claim 1, which comprises reacting a 9-[(substituted glycyl)amido]-7-(substituted)-8-(substituted)-6-demethyl-6-deoxytetracycline of the formula:



I

according to Claim 1 with a primary amine of the formula R^5NH_2 or a secondary amine of the formula



in the presence of formaldehyde.

14. Use of a compound according to Claim 1 for the preparation of a medicament for the prevention, treatment or

control of bacterial infections in warm-blooded animals.

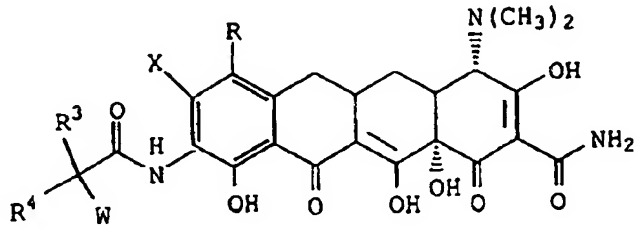
15. A pharmaceutical composition of matter comprising a pharmacologically effective amount of a compound according to Claim 1 in association with a pharmaceutically acceptable carrier.

16. A veterinary composition which comprises a pharmacologically effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

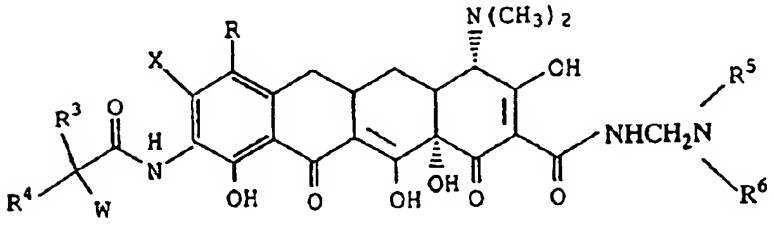
17. Use of a compound according to Claim 1 for the preparation of a medicament for the prevention, treatment or control of bacterial infections in warm-blooded animals caused by bacteria having the TetM and TetK resistant determinants.

Patentansprüche

1. Verbindung der Formel:



I



II

worin:

X ausgewählt wird aus Trifluormethansulfonyloxy, Brom, Chlor, Fluor und Iod;
R ausgewählt wird aus

(i) Wasserstoff, Brom, Chlor, Fluor und Iod; und
(ii) $-NR^1R^2$, vorausgesetzt, dass wenn R = $-NR^1R^2$ und

(a) R^1 = Wasserstoff, dann R^2 = Methyl, Ethyl, n-Propyl, 1-Methylethyl, n-Butyl, 1-Methylpropyl, 2-Methylpropyl oder 1,1-Dimethylethyl; oder
(b) R^1 = Methyl oder Ethyl, dann R^2 = Methyl, Ethyl, n-Propyl, 1-Methylethyl, n-Butyl, 1-Methylpropyl oder 2-Methylpropyl; oder
(c) R^1 = n-Propyl, dann R^2 = n-Propyl, 1-Methylethyl, n-Butyl, 1-Methylpropyl oder 2-Methylpropyl; oder

(d) R^1 = 1-Methylethyl, dann R^2 = n-Butyl, 1-Methylpropyl oder 2-Methylpropyl; oder
(e) R^1 = n-Butyl, dann R^2 = n-Butyl, 1-Methylpropyl oder 2-Methylpropyl; oder
(f) R^1 = 1-Methylpropyl, dann R^2 = 2-Methylpropyl;

R^3 ausgewählt wird aus

Wasserstoff;
grader oder verzweigter (C_1-C_6)Alkylgruppe, ausgewählt aus Methyl, Ethyl, Propyl, Isopropyl, Butyl, Isobutyl, Pentyl, Hexyl, Heptyl und Octyl;
α-Mercapto(C_1-C_4)alkylgruppe, ausgewählt aus Mercaptomethyl, α-Mercaptoethyl, α-Mercapto-1-methyl-ethyl, α-Mercaptopropyl und α-Mercaptobutyl;
α-Hydroxy(C_1-C_4)alkylgruppe, ausgewählt aus Hydroxymethyl, α-Hydroxyethyl, α-Hydroxy-1-methylethyl, α-Hydroxypropyl und α-Hydroxybutyl;
Carboxyl (C_1-C_8) alkylgruppe;
(C_6-C_{10})Arylgruppe, ausgewählt aus Phenyl, α-Naphthyl und β-Naphthyl;
substituierter (C_6-C_{10})Arylgruppe (Substitution ausgewählt aus Hydroxy, Halogen, (C_1-C_4)Alkoxy, Trihalogen-(C_1-C_3)Alkyl, Nitro, Amino, Cyano, (C_1-C_4)Alkoxycarbonyl, (C_1-C_3)Alkylamino und Carboxy);
(C_7-C_9)Aralkylgruppe, ausgewählt aus Benzyl, 1-Phenylethyl, 2-Phenylethyl und Phenylpropyl;
substituierter (C_7-C_9)Aralkylgruppe [Substitution ausgewählt aus Halogen, (C_1-C_4)Alkyl, Nitro, Hydroxy, Amino, mono- oder di-substituiertem (C_1-C_4)Alkylamino, (C_1-C_4)Alkoxy, (C_1-C_4)Alkylsulfonyl, Cyano und Carboxyl];

R^4 ausgewählt wird aus Wasserstoff und (C_1-C_6)Alkyl, ausgewählt aus Methyl, Ethyl, Propyl, Isopropyl, Butyl, Isobutyl, Pentyl und Hexyl;

Wenn R^3 nicht das gleiche wie R^4 darstellt, kann die Stereochemie des asymmetrischen Kohlenstoffs (also des Kohlenstoffs, der den W-Substituenten trägt) entweder das Racemat (DL) oder die einzelnen Enantiomere (L oder D) sein;

W ausgewählt wird aus

Amino;
Hydroxylamino;
(C_1-C_{12}) grader oder verzweigter Alkyl-monosubstituierter Aminogruppe, Substitution ausgewählt aus Methyl, Ethyl, n-Propyl, 1-Methylethyl, n-Butyl, 1-Methylpropyl, 2-Methylpropyl, 1,1-Dimethylethyl, n-Pentyl, 2-Methylbutyl, 1,1-Dimethylpropyl, 2,2-Dimethylpropyl, 3-Methylbutyl, n-Hexyl, 1-Methylpentyl, 1,1-Dimethylbutyl, 2,2-Dimethylbutyl, 3-Methylpentyl, 1,2-Dimethylbutyl, 1,3-Dimethylbutyl, 1-Methyl-1-ethylpropyl, Heptyl, Octyl, Nonyl, Decyl, Undecyl und Dodecyl und den Diastereomeren und Enantiomeren der besagten verzweigten Alkyl-monosubstituierten Aminogruppe;
(C_3-C_8)Cycloalkyl-monosubstituierter Aminogruppe, Substitution ausgewählt aus Cyclopropyl, trans-1,2-Dimethylcyclopropyl, cis-1,2-Dimethylcyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Cycloheptyl, Cyclooctyl, Bicyclo[2.2.1]hept-2-yl und Bicyclo[2.2.2]oct-2-yl und den Diastereomeren und Enantiomeren des besagten (C_3-C_8)Cycloalkyl-monosubstituierten Amino;
[(C_4-C_{10})Cycloalkyl]alkyl-monosubstituierter Aminogruppe, Substitution ausgewählt aus (Cyclopropyl)methyl, (Cyclopropyl)ethyl, (Cyclobutyl)methyl, (trans-2-Methylcyclopropy)methyl, und (cis-2-Methyl-cyclobutyl)methyl;
(C_3-C_{10})Alkenyl-monosubstituierter Aminogruppe, Substitution ausgewählt aus Allyl, 3-Butenyl, 2-Butenyl (cis oder trans), 2-Pentenyl, 4-Octenyl, 2,3-Dimethyl-2-butenyl, 3-Methyl-2-butenyl, 2-Cyclopentenyl und 2-Cyclohexenyl;
(C_6-C_{10})Aryl-monosubstituierter Aminogruppe; Substitution ausgewählt aus Phenyl and Naphthyl; (C_7-C_{10})Aralkylaminogruppe; Substitution ausgewählt aus Benzyl, 2-Phenylethyl, 1-Phenylethyl, 2-(Naphthyl)methyl, 1-(Naphthyl)methyl und Phenylpropyl;
substituierter (C_6-C_{10})Aryl-monosubstituierter Aminogruppe, [Substitution ausgewählt aus (C_1-C_5)Acyl, (C_1-C_5)Acylamino, (C_1-C_4)Alkyl, mono- oder disubstituiertem (C_1-C_8)Alkylamino, (C_1-C_4)-Alkoxy, (C_1-C_4) Alkoxycarbonyl, (C_1-C_4)Alkylsulfonyl, Amino, Carboxy, Cyano, Halogen, Hydroxy, Nitro und Trihalogen (C_1-C_3)Alkyl];
grader oder verzweigter symmetrischer disubstituierter (C_2-C_{14})Alkylaminogruppe, Substitution ausgewählt aus Dimethyl, Diethyl, Diisopropyl, Di-n-propyl, Dibutyl und Diisobutyl;
symmetrisch disubstituierter (C_3-C_{14})-Cycloalkylaminogruppe, Substitution ausgewählt aus Dicyclopropyl, Dicyclobutyl, Dicyclopentyl, Dicyclohexyl und Dicycloheptyl;

grader oder verzweigter asymmetrischer disubstituierter (C_3-C_{14})Alkylaminogruppe, worin die gesamte Anzahl an Kohlenstoffen in der Substitution nicht mehr als 14 beträgt;
asymmetrisch disubstituierter (C_4-C_{14})Cycloalkyl-aminogruppe, worin die gesamte Anzahl an Kohlenstoffen in der Substitution nicht mehr als 14 beträgt;
(C_2-C_8)Azacycloalkyl und substituierter (C_2-C_8) Azacycloälkylgruppe, Substitution ausgewählt aus Aziridinyl, Azetidinyl, Pyrrolidinyl, Piperidinyl, 4-Methylpiperidinyl, 2-Methylpyrrolidinyl, cis-3,4-Dimethylpyrrolidinyl, trans-3,4-Dimethylpyrrolidinyl, 2-Azabicyclo[2.1.1]-hex-2-yl, 5-Azabicyclo[2.1.1]hex-5-yl, 2-Azabicyclo[2.2.1]hept-2-yl, 7-Azabicyclo[2.2.1]hept-7-yl, 2-Azabicyclo[2.2.2]oct-2-yl und den Diastereomeren und Enantiomeren der besagten (C_2-C_8)Azacycloalkyl- und substituierten (C_2-C_8)Azacycloalkylgruppe;
1-Azaoxacycloalkyl, ausgewählt aus Morpholinyl und 1-Aza-5-oxocycloheptane;
substituierter 1-Azaoxacycloalkylgruppe, Substitution ausgewählt aus 2- (C_1-C_3)Alkylmorpholinyl, 3-(C_1-C_3)Alkylisoxazolidinyl, Tetrahydrooxazinyl und 3,4-Dihydrooxazinyl;
[1,n]-Diazacycloalkyl und substituierter [1,n]-Diazacycloalkylgruppe, ausgewählt aus Piperazinyl, 2-(C_1-C_3)Alkyl-piperazinyl, 4-(C_1-C_3)Alkylpiperazinyl, 2,4-Dimethyl-piperazinyl, 4-(C_1-C_4)Alkoxypiperazinyl, 4-(C_6-C_{10})-Aryloxypiperazinyl, 4-Hydroxypiperazinyl, 2,5-Diaza-bicyclo[2.2.1]hept-2-yl, 2,5-Diaza-5-methylbicyclo-[2.2.1]hept-2-yl, 2,3-Diaza-3-methylbicyclo[2.2.2]oct-2-yl, 2,5-Diaza-5,7-dimethylbicyclo [2.2.2]oct-2-yl und den Diastereomeren oder Enantiomeren der besagten [1,n]-Diaza-cycloalkyl- und substituierten [1,n]-Diazacycloalkylgruppe;
1-Azathiacycloalkyl und substituierter 1-Azathiacycloalkylgruppe, ausgewählt aus Thiomorpholinyl, 2-(C_1-C_3)-Alkylthiomorpholinyl und 3-(C_3-C_6)Cycloalkylthio-morpholinyl;
N-Azolyl und substituierter N-Azolylgruppe, ausgewählt aus 1-Imidazolyl, 2-(C_1-C_3)Alkyl-1-imidazolyl, 3-(C_1-C_3)Alkyl-1-imidazolyl, 1-Pyrrolyl, 1-Pyrazolyl, 2-(C_1-C_3)Alkyl-1-pyrrolyl, 3-(C_1-C_3)Alkyl-1-pyrazolyl, Indolyl, 1-(1,2,3-Triazolyl), 4-(C_1-C_3)Alkyl-1-(1,2,3-triazolyl), 5-(C_1-C_3)Alkyl-1-(1,2,3-triazolyl) 4-(1,2,4-Triazolyl, 1-Tetrazolyl, 2-Tetrazolyl und Benzimidazolyl;
(heterocyclischer) Aminogruppe, ausgewählt aus 2- oder 3-Furanylamino, 2- oder 3-Thienylamino, 2-, 3- oder 4-Pyridylamino, 2- oder 5-Pyridazinylamino, 2-Pyrazinylamino, 2-(Imidazolyl)amino, (Benzimidazolyl)amino und (Benzothiazolyl)amino und substituierter (heterocyclischer) Aminogruppe, wie oben definiert, mit Substitution ausgewählt aus gradem oder verzweigtem (C_1-C_6)Alkyl;
(heterocyclischer) Methylaminogruppe, ausgewählt aus 2-oder 3-Furylmethylamino, 2- oder 3-thienyl-methylamino, 2-, 3-oder 4-Pyridylmethylamino, 2- oder 5-Pyridazinylmethylamino, 2-Pyrazinylmethylamino, 2-(Imidazolyl)methylamino, (Benzimidazolyl)methylamino und (Benzothiazolyl)methylamino und substituiertem (heterocyclischen) Methylamino, wie oben definiert, mit Substitution ausgewählt aus gradem oder verzweigtem (C_1-C_6)Alkyl;
Carboxy(C_2-C_4)Alkylaminogruppe, ausgewählt aus Aminoessigsäure, α-Aminopropionsäure, β-Aminopropionsäure, α-Buttersäure und β-Aminobuttersäure und den Enantiomeren der besagten Carboxy(C_2-C_4)Alkylaminogruppe;
(C_1-C_4)Alkoxycarbonylaminogruppe, Substitution ausgewählt aus Methoxycarbonyl, Ethoxycarbonyl, Allyloxycarbonyl, Propoxycarbonyl, Isoproproxycarbonyl, 1,1-Dimethylethoxycarbonyl, n-Butoxycarbonyl und 2-Methylpropoxycarbonyl;
(C_1-C_4)Alkoxyaminogruppe, Substitution ausgewählt aus Methoxy, Ethoxy, n-Propoxy, 1-Methylethoxy, n-Butoxy, 2-Methylpropoxy und 1,1-Dimethylethoxy;
(C_3-C_8)Cycloalkoxyaminogruppe, ausgewählt aus Cyclopropoxy, trans-1,2-Dimethyl-cyclopropoxy, cis-1,2-Dimethylcyclopropoxy, Cyclobutoxy, Cyclopentoxy, Cyclohexoxy, Cycloheptoxy, Cyclooctoxy, Bicyclo-[2.2.1]hept-2-yloxy, Bicyclo[2.2.2]oct-2-yloxy und den Diastereomeren und Enantiomeren der besagten (C_3-C_8)Cycloalkoxyaminogruppe;
und
(C_6-C_{10})Aryloxyaminogruppe, ausgewählt aus Phenoxyamino, 1-Naphthyloxyamino und 2-Naphthyloxyamino; (C_7-C_{11})Arylalkoxyaminogruppe, Substitution ausgewählt aus Benzyloxy, 2-Phenylethoxy, 1-Phenylethoxy, 2-(Naphthyl)methoxy, 1-(Naphthyl)methoxy und Phenylpropoxy;

R^5 und R^6 unabhängig ausgewählt werden aus

(i) Wasserstoff, unter der Voraussetzung, dass R^5 und R^6 nicht beide Wasserstoff darstellen können;
(ii) grader oder verzweigter (C_1-C_3)-Alkylgruppe, ausgewählt aus Methyl, Ethyl, n-Propyl oder 1-Methylethyl;
(iii) (C_6-C_{10})Arylgruppe, ausgewählt aus Phenyl, α-Naphthyl oder β-Naphthyl;
(iv) (C_7-C_9)Aralkylgruppe, wie Benzyl, 1-Phenylethyl, 2-Phenyl oder Phenylpropyl
(v) einer heterocyclischen Gruppe, ausgewählt aus einem fünf-gliedrigen aromatischen oder gesättigten

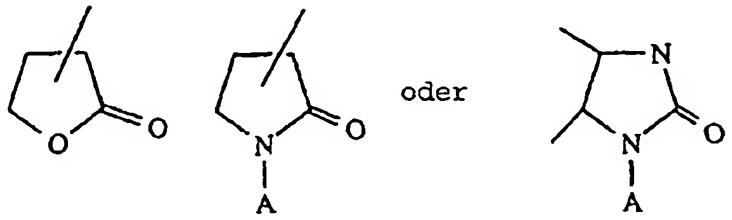
Ring mit einem N-, O-, S- oder Se-Heteroatom, gegebenenfalls mit einem daran kondensierten Benzo- oder Pyridoring:

Z = N, O, S oder Se,
wie Pyrrolyl, N-Methylindolyl, Indolyl, 2-Pyrrolidinyl, 3-Pyrrolidinyl, 2-Pyrrolinyl, Tetrahydrofuranyl, Furanyl, Benzofuranyl, Tetrahydrothienyl, Thienyl, Benzothienyl oder Selenazolyl,

(vi) einem fünf-gliedrigen aromatischen Ring mit zwei N- , O-, S- oder Se-Heteroatomen, gegebenenfalls mit einem daran kondensierten Benzo- oder Pyridoring:

Z oder Z^1 = N, O, S oder Se,
wie Imidazolyl, Pyrazolyl, Benzimidazolyl, Oxazolyl, Benzoxazolyl, Indazolyl, Thiazolyl, Benzothiazolyl, 3-Alkyl-3H-imidazo[4,5-b]pyridyl oder Pyridylimidazolyl.

(vii) einem fünf-gliedrigen gesättigten Ring mit einem oder zwei N-, O-, S- oder Se-Heteroatomen und einem angrenzend angehängten O-Heteroatom:



(worin A ausgewählt wird aus Wasserstoff; gradem oder verzweigtem (C_1-C_4)Alkyl; C_6-Aryl, substituiertem C_6-Aryl (Substitution ausgewählt aus Halogen, (C_1-C_4)Alkoxy, Trihalogen(C_1-C_3)alkyl, Nitro. Amino, Cyano, (C_1-C_4)Alkoxycarbonyl, (C_1-C_3)Alkylamino oder Carboxy); (C_7-C_9)Aralkylgruppe, ausgewählt aus Benzyl, 1-Phenylethyl, 2-Phenylethyl oder PhenylproPYl);
wie γ-Butyrolactam, γ-Butyrolacton, Imidazolidinon oder N-Aminoimidazolidinon.

(viii) oder einem sechs-gliedrigen aromatischen Ring mit einem bis drei N-Heteroatomen, wie Pyridyl, Pyridazinyl, Pyrazinyl, sym-Triazinyl, asym-Triazinyl, Pyrimidinyl oder (C_1-C_3)Alkylthiopyridazinyl,

(ix) oder einem sechs-gliedrigen gesättigten Ring mit einem oder zwei N-, O-, S- oder Se-Heteroatomen und einem angrenzend angehängten O-Heteroatom, wie 2,3-Dioxo-1-piperazinyl, 4-Ethyl-2,3-dioxo-1-piperazinyl. 4-Methyl-2,3-dioxo-1-piperazinyl. 4-Cyclopropyl-2-dioxo-1-piperazinyl, 2-Dioxomorpholinyl und 2-Dioxothiomorpholinyl;

(x) -$(CH_2)_n$COOR^7, wo n = 0-4 und R^7 ausgewählt wird aus Wasserstoff; grader oder verzweigter (C_1-C_3) Alkylgruppe, ausgewählt aus Methyl, Ethyl, n-Propyl oder 1-Methylethyl;
oder

(xi) (C_6-C_{10})Arylgruppe, ausgewählt aus Phenyl, α-Naphthyl oder β-Naphthyl;

oder R^5 und R^6 zusammengenommen für $-(CH_2)_2B(CH_2)_2-$ stehen, worin B ausgewählt wird aus $(CH_2)_n$ und n = 0-1, -NH, $-N(C_1-C_3)$Alkyl [grade oder verzweigt], $-N(C_1-C_4)$Alkoxy, Sauerstoff, Schwefel oder substituierten ähnlichen Substanzen, ausgewählt aus (L oder D)-Prolin, Ethyl(L oder D)-prolinat;

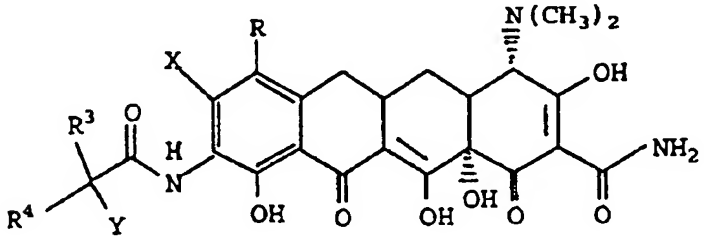
und den pharmakologisch annehmbaren organischen und anorganischen Salzen oder Metallkomplexen.

2. Verbindung gemäß Anspruch 1, worin:

X Chlor, Fluor oder Trifluormethansulfonyloxy darstellt;
R ausgewählt wird aus Wasserstoff, Chlor, Iod oder $-NR^1R^2$, worin R^1 und R^2 unabhängig Methyl oder Ethyl darstellen,
R^3 und R^4 unabhängig Wasserstoff, Methyl und Ethyl darstellen, und wenn R^3 nicht für das gleiche wie R^4 steht, kann die Stereochemie des asymmetrischen Kohlenstoffs (also des Kohlenstoffs, welcher den W-Substituenten trägt) entweder das Racemat (DL) oder die einzelnen Enantiomere (L oder D) sein;
W ausgewählt wird aus Amino; Methylamino, Ethylamino, n-Propylamino, 1-Methylethylamino, n-Butylamino, 1-Methylpropylamino, Cyclopropylamino, Cyclobutylamino, Pyrrolidinyl, Piperidinyl, 4-Methylpiperidinyl, Morpholinyl, Piperazinyl, 4-(C_1-C_3)-Alkylpiperazinyl-1-imidazolyl, 2-(C_1-C_3)Alkyl-1-imidazolyl, 3-(C_1-C_3)Alkyl-1-imidazolyl, 2-, 3- oder 4-Pyridylmethylamino, Carboxy(C_2-C_4)alkylaminogruppen, ausgewählt aus Aminoessigsäure, α-Aminopropionsäure, β-Aminopropionsäure, α-Buttersäure und β-Aminobuttersäure und den Enantiomeren der besagten Carboxy(C_2-C_4) alkylaminogruppe;
R^5 und R^6 unabhängig ausgewählt werden aus Wasserstoff, Methyl, Ethyl, n-Propyl und 1-Methylethyl; unter der Voraussetzung, dass R^5 und R^6 nicht beide Wasserstoff darstellen können; oder R^5 und R^6 stehen zusammengenommen für $-(CH_2)_2B(CH_2)_2-$, worin B ausgewählt wird aus $(CH_2)_n$ und n = 0-1, -NH, $-N(C_1-C_3)$Alkyl [grade oder verzweigt], $-N(C_1-C_4)$Alkoxy, Sauerstoff, Schwefel oder substituierten ähnlichen Substanzen, ausgewählt aus (L oder D)-Prolin, Ethyl(L oder D)-prolinat;

und den pharmakologisch annehmbaren organischen und anorganischen Salzen oder Metallkomplexen.

3. Verbindung der Formel (III):



III

worin:

Y ausgewählt wird aus Brom, Chlor, Fluor und Iod; und
R, X, R^3 und R^4 wie in Anspruch 1 definiert sind.

4. Verbindung gemäß Anspruch 3, worin:

Y ausgewählt wird aus Brom, Chlor, Fluor und Iod;
X Trifluormethansulfonyloxy, Chlor oder Fluor darstellt;
R ausgewählt wird aus Wasserstoff; Chlor, Iod oder $-NR^1R^2$, worin R^1 und R^2 jeweils unabhängig Methyl oder Ethyl darstellen;
R^3 ausgewählt wird aus Wasserstoff, Methyl und Ethyl;
R^4 ausgewählt wird aus Wasserstoff, Methyl und Ethyl;

wenn R^3 nicht das gleiche darstellt wie R^4, die Stereochemie des asymmetrischen Kohlenstoffs (also des Kohlenstoffs, welcher den W-Substituenten trägt) entweder das Racemat (DL) oder die einzelnen Enantiomere (L oder D) sein kann; und den pharmakologisch annehmbaren organischen oder anorganischen Salzen oder Metallkomplexen.

5. Verbindung gemäß Anspruch 1-3, worin besagte Salze oder Metallkomplexe umfassen: Chlorwasserstoff-, Bromwasserstoff-, Iodwasserstoff-, Phosphorsäure-, Salpetersäure-, Sulfat, Acetat, Benzoat, Citrat, Cystein oder andere Aminosäuren, Fumarat, Glycolat, Maleat, Succinat, Tartrat, Alkylsulfonat, Arylsulfonat, Aluminium, Calcium, Eisen, Magnesium oder Mangan.

6. Verbindung gemäß Anspruch 1, welche eine der folgenden ist:

[4S-(4α,12aα)]-8-Chlor-4-(dimethylamino)-9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,-6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamiddisulfat
[Verbindung der Formel I, worin R = H; X = Cl; R^3 = H; R^4 = H; W = NMe_2; Disulfatsalz]
[4S-(4α,12aα)]-8-Chlor-4-(dimethylamino)-9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,-6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid
[Verbindung der Formel I, worin R = H; X = Cl; W = MMe_2; R^3 = H; R^4 = H]
[4S-(4α,12aα)]-8-Chlor-4,7-(dimethylamino)-9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,-12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid
[Verbindung der Formel I, worin R = NMe_2; X = Cl; W = NMe_2; R^3 = H; R^4 = H]
[4S-(4α,12aα)]-9-[[(Butylamino)acetyl]amino]-8-Chlor-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid
[Verbindung der Formel I, worin R = NMe_2; X = Cl; W = NHBu; R^3 = H; R^4 = H]
[7S-(7α, 10α)]-N-[9-(Aminocabonyl)-3-chlor-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1H-pyrrol-1-acetamid
[Verbindung der Formel I, worin R = NMe_2; X = Cl; W = 1H-Pyrrol-1-yl; R^3 = H; R^4 = H]
[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chlor-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1H-pyrazol-1-acetamid
[Verbindung der Formel I, worin R = NMe_2; X = Cl; W = 1H-Pyrazol-1-yl; R^3 = H; R^4 = H]
[4S-(4α, 12aα)]-8-Chlor-4,7-bis(dimethylamino)-9-[[[(1,1-dimethylethyl)amino]acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid
[Verbindung der Formel I, worin R = NMe_2; X = Cl; W = NHTBu; R^3 = H; R^4 = H]
[4S-(4α,12aα)]-8-Chlor-9-[[(cyclopropylamino)acetyl]amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12, 12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid
[Verbindung der Formel I, worin R = NMe_2; X = Cl; W = Cyclopropylamino; R^3 = H; R^4 = H]
[4S-(4α,12aα)]-8-Chlor-9-[[[(cyclobutyloxy)amino]acetyl]amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,-11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid
[Verbindung der Formel I, worin R = NMe_2; X = Cl; W = Cyclobutyloxyamino; R^3 = H; R^4 = H]
[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chlor-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1-pyrrolidinacetamid
[Verbindung der Formel I, worin R = NMe_2; X = Cl; W = Pyrrolidin-1-yl; R^3 = H; R^4 = H]
[4S-(4α,12aα)]-8-Chlor-4,7-bis(dimethylamino)-1,4,4a,5,5a, 6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[(propylamino)]acetyl]amino]-2-naphthacencarboxamid
[Verbindung der Formel I, worin R = NMe_2; X = Cl; W = NHPr; R^3 = H; R^4 = H]
[4S-(4α,12aα)]-8-Chlor-4,7-bis(dimethylamino)-1,4,4a,5,5a, 6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[1-oxo-2-(propylamino)propyl]amino]-2-naphthacencarboxamid
[Verbindung der Formel I, worin R = NMe_2 X = Cl; W = NHPr; R^3 = H; R^4 = CH_3]
[4S-(4α,12aα)]-4,7-Bis(dimethylamino)-9-[[(dimethyl-amino)acetyl]amino]-8-fluor-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12, 12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid
[Verbindung der Formel I, worin R = NMe_2; X = F; W = NMe_2; R^3 = H; R^4 = H]
[4S-(4α,12aα)]-9-[[(Butylamino)acetyl]amino]-8-chlor-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxonaphthacencarboxamid-dihydrochlorid
[Verbindung der Formel I, worin R = H; X = Cl; W = NHBu; R^3 = H; R^4 = H; Hydrochloridsalz]
[4S-(4α,12aα)]-8-Chlor-4-(dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(propylamino)acetyl]amino]-2-naphthacencarboxamid-dihydrochlorid
[Verbindung der Formel I, worin R = H; X = Cl; W = NHPr; R^3 = H; R^4 = H; Hydrochloridsalz]
[4S-(4α,12aα)]-8-Chlor-4-(dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-

dioxo-9-[[(pentylamino)acetyl]amino]-2-naphthacencarboxamid-dihydrochlorid
[Verbindung der Formel I, worin R = H; X = Cl; W = Phenylamino; R^3 = H; R^4 = H; Hydrochloridsalz]
[4S-(4α,12aα)]-8-Chlor-4-(dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(methylamino)acetyl]amino]-2-naphthacencarboxamid-dihydrochlorid
[Verbindung der Formel I, worin R = H; X = Cl; W = NHMe; R^3 = H; R^4 = H; Hydrochloridsalz]
[4S-(4α,12aα)]-8-Chlor-9-[[(cyclopropylmethylamino)acetyl]amino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamiddihydrochlorid
[Verbindung der Formel I, worin R = H; X = Cl; W = Cyclopropylmethylamino; R^3 = H; R^4 = H; Hydrochloridsalz]
[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chlor-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1-pyrrolidinacetamid-dihydrochlorid
[Verbindung der Formel I, worin R = H; X = Cl; W = Pyrrolidin-1-yl; R^3 = H; R^4 = H; Hydrochloridsalz]
[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chlor-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1-piperidinacetamid-dihydrochlorid
[Verbindung der Formel I, worin R = H; X = Cl; W = Piperidin-1-yl; R^3 = H; R^4 = H; Hydrochloridsalz]
7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chlor-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-5-azabicyclo[2.1.1]hexan-5-acetamiddihydrochlorid
[Verbindung der Formel I, worin R = H; X = Cl; W = Azabicyclo-[2.1.1]hex-5-yl; R^3= H; R^4 = H; Hydrochloridsalz]
[4S-(4α,12aα)]-8-Chlor-9-[[(cyclobutylamino)acetyl]-amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid-dihydrochlorid
[Verbindung der Formel I, worin R = H; X = Cl; W = Cyclobutylamino; R^3 = H; R^4 = H; Hydrochloridsalz]
[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chlor-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-α-ethyl-1H-imidazol-1-acetamiddihydrochlorid
[Verbindung der Formel I, worin R = H; X = Cl; W = 1-H-Imidazol-1-yl; R^3 = H; R^4 = Et; Hydrochloridsalz]
[4S-(4α,12aα)]-8-Chlor-9-[[2-(diethylamino)-1-oxopropyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid
[Verbindung der Formel I, worin R = H; X = Cl; W = NEt_2; R^3 = H; R^4 = H]
[4S-(4α,12aα)]-8-Chlor-4-(dimethylamino)-9-[[(dimethylamino) (2-fluorphenyl)acetyl]amino]-1,4,4a,5,-5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid
[Verbindung der Formel I, worin R = H; X = Cl; W = NMe_2; R^3 = 2-Fluorphenyl; R^4 = H]
[4S-(4α,12aα)]-8-Chlor-4-(dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-1,-11-dioxo-9-[[1-oxo-4-phenyl-2-[(phenylmethoxy)amino]butyl]amino]-2-naphthacencarboxamid
[Verbindung der Formel I, worin R = H; X = Cl; W = -$NHCH_2$Ph; R^3 = 2-Phenylethyl; R^4 = H]
[4S-(4α,12aα)] -4-(Dimethylamino)-9-[[(dimethylamino)acetyl]amino]-8-fluor-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid
[Verbindung der Formel I, worin R = H; X = F; W = NMe_2; R^3 = H; R^4 = H]
[4S-(4α,12aα)]-4-(Dimethylamino)-8-fluor-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(propylamino)acetyl]amino]-2-naphthacencarboxamid
[Verbindung der Formel I, worin R = H; X = F; W = NHPr; R^3 = H; R^4 = H]
[4S-(4α,12aα)1-4-(Dimethylamino)-9-[[(dimethylamino)-acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-8-[[(trifluormethyl)sulfonyl]oxy]-2-naphthacencarboxamid
[Verbindung der Formel I, worin R = H; X = O-SO_2-CF_3; W = NMe_2; R^3 = H; R^4 = H]

7. Verbindung gemäß Anspruch 3, welche eine der folgenden ist:

[4S-(4α,12aα)]-9-[(Chloracetyl)amino]-8-chlor-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid
[Verbindung der Formel III, worin R = NMe_2; X = Cl; R^3 = H; R^4 = H; Y = Br]
[4S-(4α,12aα)]-9-[(Bromacetyl)amino]-8-chlor-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid
[Verbindung der Formel III, worin R = NMe_2; X = Cl; R^3 = H; R^4 = H; Y = Br]
[4S-(4α,12aα)]-9-[(α-Brompropionyl)amino]-8-chlor-4,7-bis (dimethylamino)-1,4,4a,5,5a,-6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid
[Verbindung der Formel III, worin R = NMe_2; X = Cl; R^3 = H; R^4 = Me; Y=Br]
[4S-(4α,12aα)]-9-[(α-Bromphenylacetyl)amino]-8-chlor-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid
[Verbindung der Formel III, worin R = NMe_2; X = Cl; R^4 = H; R^3 = Ph; Y = Br]

[4S-(4α,12aα)]-9-[(α-Brom-2,2-dimethylbutiryl)amino]-8-chlor-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid
[Verbindung der Formel III, worin R = NMe_2; X = Cl, R^3= Isopropyl; R^4 = H; Y = Br]
[4S-(4α,12aα)]-9-[(α-Brom-(2,4-difluorphenyl)acetyl)amino]-8-chlor-4,7-bis(dimethylamino)-1,4,4a,5,-5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid
[Verbindung der Formel III, worin R = NMe_2; X = Cl; R^3 = 2,4-Difluorphenyl; R^4 = H; Y = Br]
[4S-(4α,12aα)]-9-[(Bromacetyl)amino]-4,7-bis-(dimethylamino)-8-fluor-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid
[Verbindung der Formel III, worin R = NMe_2; X = F; R^3 = H; R^4 = H; Y = Br]
[4S-(4α,12aα)]-9-[(Bromacetyl)amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-8-[[(trifluormethyl)-sulfonyl]oxy]-2-naphthacencarboxamid
[Verbindung der Formel III, worin R = NMe_2; X = OSO_2CF_3; R^3 = H; R^4 = H; Y = Br; Hydrochloridsalz]
[4S-(4α,12aα)]-9-[(Chloracetyl)amino]-8-chlor-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamid-hydrochlorid
[Verbindung der Formel III, worin R = H; X = Cl; R^3 = H; R^4 = H; Y = Cl; Hydrochloridsalz]
[4S-(4α,12aα)]-9-[(Bromacetyl)amino]-8-chlor-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid-hydrobromid
[Verbindung der Formel III, worin R = H; X = Cl; R^3 = H; R^4 = H; Y = Br; Hydrobromidsalz]
[4S-(4α,12aα)]-9-[(2-Chlorpropionyl)amino]-8-chlor-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid-hydrochlorid
[Verbindung der Formel III, worin R = H; X = Cl; R^3 = H; R^4 = Me; Y = Cl; Hydrochloridsalz]
[4S-(4α,12aα)]-9-[(2-Chlorbutirylamino]-8-chlor-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid-hydrochlorid
[Verbindung der Formel III, worin R = H; X = Cl; R^3 = H; R^4 = Et; Y = Cl; Hydrochloridsalz]
4S-(4α,12aα)]-9-[[(4-Hydroxyphenyl])-α-chloracetyl]-amino]-8-chlor-4-(dimethylamino)-1,4,4a,5,5a,6,11,-12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid-hydrochlorid
[Verbindung der Formel III, worin R = H; X = Cl; R^3 = 4-Hydroxyphenyl; R^4 = H; Y = Cl; Hydrochloridsalz]
[4S-(4α,12aα)]-9-[[(2-Fluorphenyl)-α-bromacetyl]-amino]-8-chlor-4-(dimethylamino)-1,4,4a,5,5a,6,11,-12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamidhydrobromid
[Verbindung der Formel III, worin R = H; X = Cl; R^3 = 2-Fluorphenyl; R^4 = H; Y = F; Hydrobromidsalz]
[4S-(4α,12aα)]-9-[(α-Brom-4-phenylbutiryl)amino]-8-chlor-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid-hydrobromid
[Verbindung der Formel III, worin R = H; X = Cl; R^3 = 2-Phenylethyl; R^4 = H; Y = Br; Hydrobromidsalz]
[4S-(4α,12aα)]-9-[(Bromacetyl)amino]-4-(dimethylamino)-8-fluor-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid
[Verbindung der Formel III, worin R = H; X = F; R^3 = H; R^4 = H; Y = Br]
[4S-(4α,12aα)]-9-[(Bromacetyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-8-[[(trifluormethyl)sulfonyl]oxy]-2-naphthacencarboxamid
[Verbindung der Formel III, worin R = H; X = OSO_2CF_3; R^3 = H; R^4 = H; Y = Br]

8. Verbindung, ausgewählt aus:

[4S-(4α,12aα)]-8-Chlor-4,7-bis(dimethylamino)-1,4,4a,5,5a, 6,11,12a-octahydro-3,10,12,12a-tetra-hydroxy-9-[[[(3-methylcyclobutyl)amino]acetyl]amino]-1,11-dioxo-2-naphthacencarboxamid
[Verbindung der Formel I, worin R = NMe_2; X = Cl; W = 3-Methylcyclobutylamino; R^3 = H; R^4 = H]
[7S-(7α,10aα)]-N-[9- (Aminocarbonyl) -3-chlor-4,7-bis-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,9,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-(3-methyl-1-pyrrolidin)-acetamid
[Verbindung der Formel I, worin R = NMe_2; X = Cl; W = 3-Methylpyrrolidin-1-yl; R^3 = H; R^4 = H]
[7S-(7α,10aα)]-N-[9- (Aminocarbonyl)-3-chlor-4,7-bis-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-a-cyclobutyl-tetrahydro-2H-1,2-isoxazin-2-acetamid
[Verbindung der Formel I, worin R = NMe_2; X = Cl; W = Tetrahydro-2H-1,2-isoxazin-2-yl; R^3 = H; R^4 = Cyclobutyl]
[4S-(4α,12aα)]-8-Chlor-4,7-bis(dimethylamino)-1,4,4a,5,5a, 6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[phenyl[(phenylmethyl)amino]acetyl]amino]-2-naphthacencarboxamid
[Verbindung der Formel I, worin R = NMe_2; X = Cl; W = Phenyl(phenylmethyl)amino; R^3 = H; R^4 = H]
[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chlor-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-α-cyclopropyl-a-methyl-1-azetidinacetamid
[Verbindung der Formel I, worin R = NMe_2; X = Cl; W = Azetidin-1-yl; R^4 = CH_3; R^3 = Cyclopropyl]

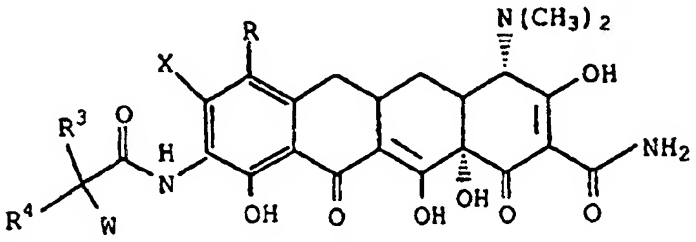
[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chlor-4,7-bis-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-α-(1,1-dimethylethyl)-(3-methyl-4-morpholin)acetamid
[Verbindung der Formel I, worin R = NMe_2; X = Cl; W = 3-Methylmorpholin-4-yl; R^3 = tBu; R^4 = H]
[4S-(4α,12aα)]-8-Chlor-9-[[(2,4-difluorphenyl)[(2-phenylethyl)amino]acetyl]amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6, 11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid
[Verbindung der Formel I, worin R = NMe_2; X = Cl; W = (2,4-Difluorphenyl)-(2-phenylethyl)amino; R^3 = H; R^4 = H]
[7S- (7α,10aα)]-N-[9- (Aminocarbonyl) -3-Chlor-4,7-bis (dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-α-(methoxyamino)-α-methyl-2-furanacetamid
[Verbindung der Formel I, worin R = NMe_2; X = Cl; W = NHOMe; R^3 = Furan-2-yl; R^4 = CH_3]
[7S-(7α,10aα)]-4-[[9-(Aminocarbonyl)-3-chlor-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-amino-3-[(1,1-dimethylethyl) amino]-4-oxobutansäure-methylester
[Verbindung der Formel I, worin R = NMe_2, X = Cl; W = -NHTBu; R^3 = CH_2COOMe; R^4 = H]
[7S-(7α,10aα)]-4-[(9-(Aminocarbonyl)-3-chlor-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-amino]-3-(dimethylamino)-4-oxobutansäure-methylester
[Verbindung der Formel I, worin R = NMe_2; X = Cl; W = NMe_2; R^3 = CH_2COOMe; R^4 = H]
[7S-(7α,10aα)]-γ-[[[9-(Aminocarbonyl)-3-chlor-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-amino]carbonyl]-1-pyrrolidinbutansäure-methylester
[Verbindung der Formel I, worin R = NMe_2; X = Cl; W = Pyrrolidin-1-yl; R^3 = CH_2CH_2COOMe; R^4 = H]
[7S-(7α,10aα)]-1-[2-[[9-(Aminocarbonyl)-3-chlor-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-1-methyl-2-oxoethyl]prolin-methylester
[Verbindung der Formel I, worin R = H; X = Cl; W = -2-Methoxycarbonyl-pyrrolidin-1-yl; R^3 = CH_3; R^4 = H]
[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chlor-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-α-(4-hydroxyphenyl)-6-methyl-2,6-diazabicyclo-[2.1.1]heptan-2-acetamid
[Verbindung der Formel I, worin R = H; X = Cl; W = 6-Methyl-2,6-diazabicyclo[2.1.1] heptan-2-yl; R^3 = hydroxyphenyl; R^4 = H]
[4S-(4α,12aα)]-8-Chlor-4-(dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[1-(4-methoxy-1-piperazinyl)-4-pentenoyl]amino]-1,11-dioxo-2-naphthacencarboxamid
[Verbindung der Formel I, worin R = H; X = Cl; W = 4-Methoxypiperazin-1-yl; R^3 = $CH_2CH_2CH{=}CH_2$; R^4 = H]
[7S-(7α,10aα)]-N-[9-(Aminocarbonyl)-3-chlor-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-α-4-pyridyl-5-azabicyclo[2.1.1]-hexan-5-acetamid
[Verbindung der Formel I, worin R = H; X = Cl; W = Azabicyclo-[2.1.1]hex-1-yl; R^3 = 4-Pyridyl; R^4 = H]

9. Verbindung, ausgewählt aus:

[4S-(4α,12aα)]-9-[(α-Bromcyclobutylacetyl)amino]-8-chlor-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12, 12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid
[Verbindung der Formel III, worin R = NMe_2; X = Cl; R^4 = H; R^3 = Cyclobutyl; Y = Br]
[4S-(4α,12aα)]-9-[(α-Brom-α-cyclopropylpropionyl)-amino]-8-chlor-4,7-bis(dimethylamino)-1,4,4a,5,5a,-6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid
[Verbindung der Formel III, worin R = MMe_2; X = Cl; R^3 = Cyclopropyl; R^4 = Me; Y = Br]
[4S-(4α,12aα)]-9-[(α-Brom-(2-furyl)propionyl)amino]-8-chlor-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid
[Verbindung der Formel III, worin R = NMe_2; X = Cl; R^3 = Furanylmethyl; R^4 = H; Y = Br]
[4S-(4α,12aα)]-9-[(α-Brom-(3-methoxycarbonyl-propionyl))-amino]-8-chlor-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid
[Verbindung der Formel III, worin R = NMe_2; X = Cl; R^3 = Methoxylcarbonylmethyl; R^4 = H; Y = Br]
[4S-(4α,12aα)]-9-[(α-Brom(4-methoxycarbonylbutiryl))amino]-8-chlor-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid
[Verbindung der Formel III, worin R = NMe_2; X = Cl; R^3 = Methoxylcarbonylethyl; R^4 = H; Y = Br]
[4S-(4α,12aα)]-9-[(2-Brom-4-pentenoyl)amino]-8-chlor-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid-hydrobromid
[Verbindung der Formel III, worin R = H; X = Cl; R^3 = $-CH_2CH{=}CH_2$; R^4 = H; Y = F; Hydrobromidsalz]
[4S-(4α,12aα)]-9-[((4-Pyridyl)-α-bromacetyl)amino]-8-chlor-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid-hydrobromid

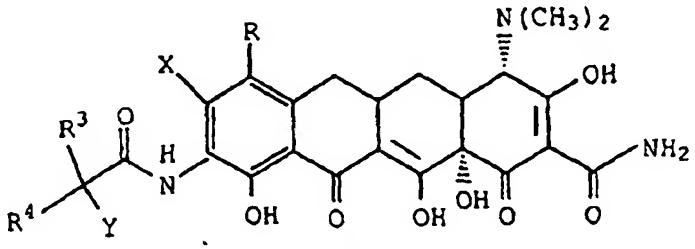
[Verbindung der Formel III, worin R = H; X = Cl; R^3 = 4-Pyridyl; R^4 = H; Y = Br; Hydrobromidsalz]

10. Verfahren zum Herstellen einer Verbindung oder seiner organischen und anorganischen Salze oder Metallkomplexe der Formel:



I

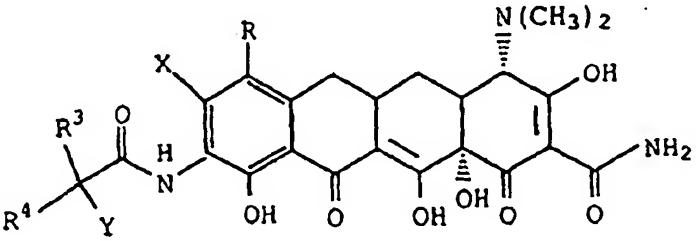
gemäß Anspruch 1, welches umfasst: Umsetzen eines 9-[(Halogenacyl)amido]-7-(substituierten)-8-(substituierten)-6-demethyl-6-deoxytetracyclins, oder seiner organischen und anorganischen Salze oder Metallkomplexe der Formel:



III

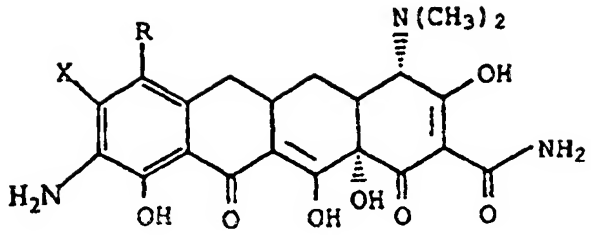
gemäß Anspruch 3, mit einem Nucleophil der Formel WH, worin W wie in Anspruch 1 definiert ist, in einem polarprotischen oder einem polar-aprotischen Lösungsmittel in einer inerten Atmosphäre.

11. Verfahren zum Herstellen einer Verbindung oder ihrer organischen und anorganischen Salze oder Metallkomplexe der Formel:

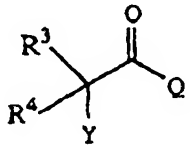


III

gemäß Anspruch 3, welches umfasst: Umsetzen eines 9-Amino-7-(substituierten)-8-(substituierten)-6-demethyl-6-deoxytetracyclins oder seiner organischen und anorganischen Salze oder Metallkomplexe der Formel:

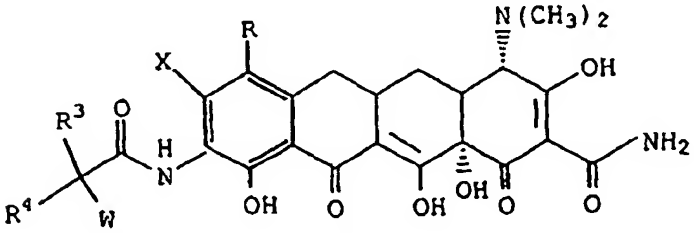


mit einem graden oder verzweigten Halogenacylhalogenid der Formel



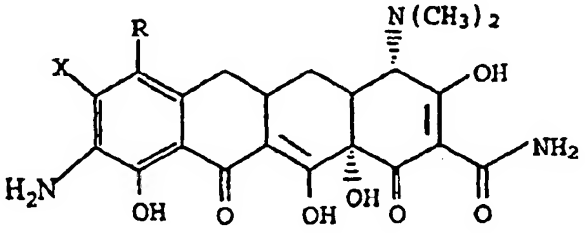
worin Y, R^3 und R^4 wie in Anspruch 1 definiert sind und Q für Halogen steht, ausgewählt aus Brom, Chlor, Iod und Fluor, in einem inerten Lösungsmittel, in einem polar-protischen Lösungsmittel in Gegenwart einer Base.

12. Verfahren zum Herstellen einer Verbindung oder seiner organischen und anorganischen Salze oder Metallkomplexe der Formel:

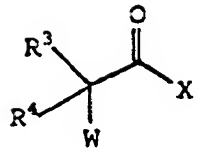


I

gemäß Anspruch 1, welches umfasst: Umsetzen eines 9-Amino-7-(substituierten)-8-(substituierten)-6-demethyl-6-deoxy-tetracyclins oder seiner organischen und anorganischen Salze oder Metallkomplexe der Formel:

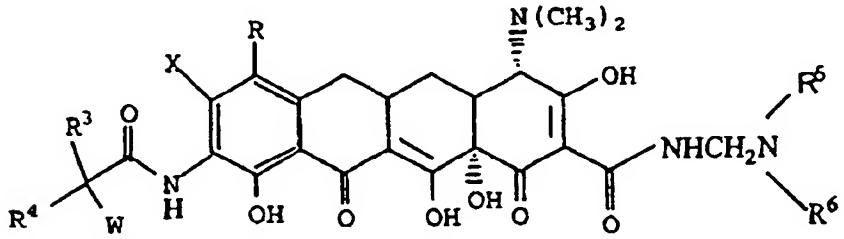


mit einem graden oder verzweigten Säurechlorid der Formel:



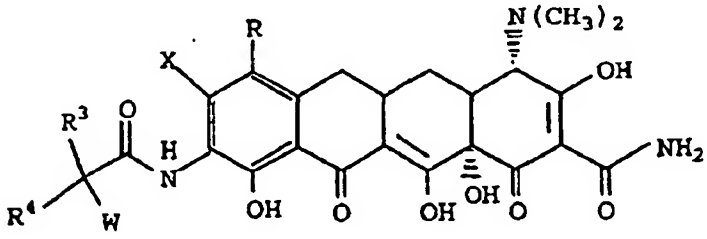
worin R^3, R^4 und W wie in Anspruch 1 definiert sind und X für Halogen steht, ausgewählt aus Brom, Chlor, Iod und Fluor, in einem geeigneten sauren Spülmittel und geeigneten Lösungsmittel.

13. Verfahren zum Herstellen einer Verbindung der Formel:



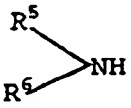
II

gemäß Anspruch 1, welches umfasst: Umsetzen eines 9-[(substituierten Glicyl)amido]-7-(substituierten)-8-(substituierten)-6-demethyl-6-deoxytetracyclins der Formel:



I

gemäß Anspruch 1, mit einem primären Amin der Formel R^5NH_2 oder einem sekundären Amin der Formel



in Gegenwart von Formaldehyd.

14. Verwendung einer Verbindung gemäß Anspruch 1 für die Herstellung einer Arznei zur Verhinderung, Behandlung oder Bekämpfung von bakteriellen Infektionen in warmblütigen Tieren.

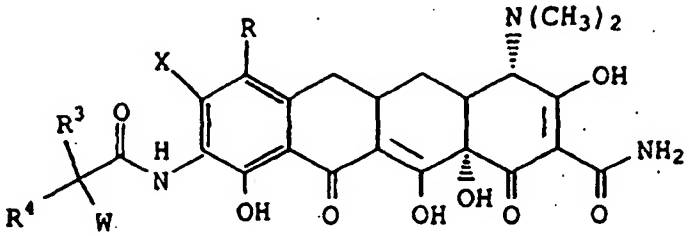
15. Pharmazeutische Zusammensetzung von Substanzen, umfassend eine pharmakologisch wirksame Menge einer Verbindung gemäß Anspruch 1 in Verbindung mit einem pharmazeutisch annehmbaren Träger.

16. Veterinäre Zusammensetzung, welche eine pharmakologisch wirksame Menge einer Verbindung nach Anspruch 1 und einen pharmazeutisch annehmbaren Träger umfasst.

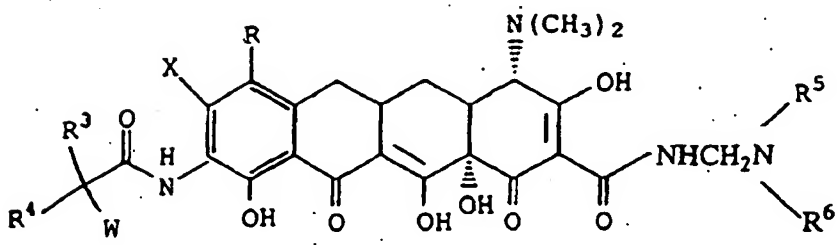
17. Verwendung einer Verbindung gemäß Anspruch 1 zur Herstellung einer Arznei zur Verhinderung, Behandlung und Bekämpfung von bakteriellen Infektionen in warmblütigen Tieren, verursacht durch Bakterien mit den TetM- und TetK-Resistenzdeterminanten.

Revendications

1. Composé de formules:



I



II

dans lesquelles:

X est sélectionné parmi un groupe trifluorométhanesulfonyloxy, le brome, le chlore, le fluor et l'iode;
R est sélectionné parmi

(i) l'hydrogène, le brome, le chlore, le fluor et l'iode; et
(ii) $-NR^1R^2$, et si R représente $-NR^1R^2$ et si

(a) R^1 représente l'hydrogène,
alors R^2 représente un groupe méthyle, éthyle, n-propyle, 1-méthyléthyle, n-butyle, 1-méthylpropyle, 2-méthylpropyle ou 1,1-diméthyléthyle; ou
(b) R^1 représente un groupe méthyle ou éthyle, alors R^2 représente un groupe méthyle, éthyle, n-propyle, 1-méthyléthyle, n-butyle, 1-méthylpropyle ou 2-méthylpropyle: ou
(c) R^1 représente un groupe n-propyle,
alors R^2 représente un groupe n-propyle, 1-méthyléthyle, n-butyle, 1-méthylpropyle ou 2-méthylpropyle; ou

(d) R^1 représente un groupe 1-méthyléthyle, alors R^2 représente un groupe n-butyle, 1-méthylpropyle ou 2-méthylpropyle;
(e) R^1 représente un groupe n-butyle,
alors R^2 représente un groupe n-butyle, 1-méthylpropyle ou 2-méthylpropyle;
(f) R^1 représente un groupe 1-méthylpropyle, alors
R^2 représente un groupe 2-méthypropyle;
R^3 est sélectionné parmi

l'hydrogène,
un groupe alkyle en C_1 à C_8 linéaire ou ramifié, sélectionné parmi
un groupe méthyle, éthyle, propyle, isopropyle, butyle, isobutyle, pentyle, hexyle, heptyle et octyle;
un groupe α-mercapto(alkyle en C_1 à C_4) sélectionné parmi un groupe mercaptométhyle, α-mercaptoéthyle, α-mercapto-1-méthyl-éthyle, α-mercapto-propyle et α-mercaptobutyle;
un groupe α-hydroxy(alkyle en C_1 à C_4) sélectionné parmi un groupe hydroxyméthyle, α-hydroxyéthyle, α-hydroxy-1-méthyléthyle, α-hydroxy-propyle et α-hydroxybutyle;
un groupe carboxy(alkyle en C_1 à C_8);
un groupe aryle en C_6 à C_{10} sélectionné parmi un groupe phényle, α-naphtyle et β-naphtyle;
un groupe aryle en C_6 à C_{10} substitué (la substitution étant sélectionnée parmi un groupe hydroxy, un halogène, un groupe alkoxy en C_1 à C_4, trihalo(alkyle en C_1 à C_3), nitro, amino, cyano, (alkoxy en C_1 à C_4)carbonyle, (alkyle en C_1 à C_3)amino et carboxy) :
un groupe aralkyle en C_7 à C_9 sélectionné parmi le benzyle, le 1-phényléthyle, le 2-phényléthyle et le phénylpropyle;
un groupe aralkyle en C_7 à C_9 substitué [la substitution étant choisie parmi un halogène, un groupe alkyle en C_1 à C_4, un groupe nitro, hydroxy, amino, (alkyle en C_1 à C_4)amino mono ou disubstitué, alkoxy en C_1 à C_4, (alkyle en C_1 à C_4)sulfonyle, cyano et carboxy];

R^4 est sélectionné parmi l'hydrogène et un groupe alkyle en C_1 à C_6 sélectionné parmi le méthyle, l'éthyle, le propyle, l'isopropyle, le butyle, l'isobutyle, le pentyle et l'hexyle;
lorsque R^3 n'est pas identique à R^4, la stéréochimie du carbone asymétrique (c'est-à-dire le carbone portant le substituant W) peut être soit le racémate (DL) soit les énantiomères individuels (L ou D) :
W est sélectionné parmi

un groupe amino;
un groupe hydroxylamino;
un groupe amino monosubstitué par un alkyle en C_1 à C_{12} linéaire ou ramifié, la substitution étant sélectionnée parmi le méthyle, l'éthyle, le n-propyle, le 1-méthyléthyle, le n-butyle, le 1-méthylpropyle, le 2-méthylpropyle, le 1,1-diméthyléthyle, le n-pentyle, le 2-méthylbutyle, le 1,1-diméthylpropyle, le 2,2-diméthylpropyle, le 3-méthylbutyle, le n-hexyle, le 1-méthylpentyle, le 1,1-diméthylbutyle, le 2,2-diméthylbutyle, le 3-méthylpentyle, le 1,2-diméthylbutyle, le 1,3-diméthylbutyle, le 1-méthyl-1-éthylpropyle, l'heptyle, l'octyle, le nonyle, le décyle, l'undécyle et le dodécyle, et les diastéréoisomères et énantiomères dudit groupe amino monosubstitué par un groupe alkyle ramifié;
un groupe amino monosubstitué par un groupe cycloalkyle en C_3 à C_8, la substitution étant sélectionnée parmi le cyclopropyle, le trans-1,2-diméthylcyclopropyle, le cis-1,2-diméthylcyclopropyle, le cyclobutyle, le cyclopentyle, le cyclohexyle, le cycloheptyle, le cyclooctyle, le bicyclo [2.2.1]-hept-2-yle et le bicyclo[2.2.2]oct-2-yle, et les diastéréoisomères et énantiomères dudit groupe amino monosubstitué par un groupe cycloalkyle en C_3 à C_8;
un groupe amino monosubstitué par un [cycloalkyle en C_4 à C_{10}]alkyle, la substitution étant sélectionnée parmi le (cyclopropyl)méthyle, le (cyclopropyl)éthyle, le (cyclobutyl)méthyle, le (trans-2-méthylcyclopropyl)méthyle et le (cis-2-méthylcyclobutyl)méthyle;
un groupe amino monosubstitué par un alcényle en C_3 à C_{10}, la substitution étant sélectionnée parmi un groupe allyle, le 3-butényle, le 2-butényle (cis ou trans), le 2-pentényle, le 4-octényle, le 2,3-diméthyl-2-butényle, le 3-méthyl-2-butényle, le 2-cyclopentényle et le 2-cyclohexényle;
un groupe amino monosubstitué par un aryle en C_6 à C_{10}, la substitution étant sélectionnée parmi le phényle et le naphtyle; un groupe (aralkyle en C_7 à C_{10})amino, la substitution étant sélectionnée parmi le benzyle, le 2-phényléthyle, le 1-phényléthyle, le 2-(naphtyl)méthyle, le 1-(naphtyl)méthyle et le phénylpropyle;

un groupe amino monosubstitué par un groupe aryle en C_6 à C_{10} substitué [la substitution étant sélectionnée parmi un groupe acyle en C_1 à C_5, un acylamino en C_1 à C_5, un alkyle en C_1 à C_4, un (alkyle en C_1 à C_8)amino monosubstitué ou disubstitué, un alkoxy en C_1 à C_4, un (alkoxy en C_1 à C_4)carbonyle, un (alkyl en C_1 à C_4) sulfonyle, un amino, carboxy, cyano, halogène, hydroxy, nitro et trihalo(alkyle en C_1 à C_3)];

un groupe (alkyle en C_2 à C_{14})amino linéaire ou ramifié disubstitué de façon symétrique, la substitution étant sélectionnée parmi un groupe diméthyle, diéthyle, diisopropyle, di-n-propyle, dibutyle et diisobutyle;

un groupe (cycloalkyle en C_3 à C_{14})amino disubstitué de façon symétrique, la substitution étant sélectionnée parmi un groupe dicyclopropyle, dicyclobutyle, dicyclopentyle, dicyclohexyle et dicycloheptyle;

un groupe (alkyle en C_3 à C_{14})amino linéaire ou ramifié) disubstitué de façon non symétrique, dans lequel le nombre total d'atomes de carbone dans la substitution n'est pas supérieur à 14;

un groupe (cycloalkyle en C_4 à C_{14})amino disubstitué de façon non symétrique, dans lequel le nombre total d'atomes de carbone de la substitution n'est pas supérieur à 14;

un groupe azacycloalkyle en C_2 à C_8 et un groupe azacycloalkyle en C_2 à C_8 substitué, la substitution étant sélectionnée parmi l'aziridinyle, l'azétidinyle, le pyrrolidinyle, le pipéridinyle, le 4-méthylpipéridinyle, le 2-méthylpyrrolidinyle, le cis-3,4-diméthylpyrrolidinyle, le trans-3,4-diméthylpyrrolidinyle, le 2-azabicyclo[2.1.1]hex-2-yle, le 5-azabicyclo[2,1,1]hex-5-yle, le 2-azabicyclo [2.2,1]-hept-2-yle, le 7-azabicyclo[2.2,1]hept-7-yle, le 2-azabicyclo-[2.2.2]oct-2-yle et les diastéréoisomères et énantiomères dudit groupe azacycloalkyle en C_2 à C_8 et dudit groupe azacycloalkyle en C_2 à C_8 substitué;

un groupe 1-azaoxacycloalkyl sélectionné parmi le morpholinyle et le 1-aza-5-oxocycloheptane;

un groupe 1-azaoxacycloalkyl substitué, la substitution étant sélectionnée parmi un groupe 2-(alkyle en C_1 à C_3)morpholinyle, un 3-(alkyle en C_1 à C_3)isoxazolidinyle, le tétrahydrooxazinyle et le 3,4-dihydrooxazinyle;

un groupe [1,n]-diazacycloalkyle et un groupe [1,n]-diazacycloalkyle substitué sélectionné parmi le pipérazinyle, un 2-(alkyle en C_1 à C_3)pipérazinyle, un 4-(alkyle en C_1 à C_3)pipérazinyle, le 2,4-diméthylpipérazinyle, un 4-(alkoxy en C_1 à C_4)pipérazinyle, un 4-(aryloxy en C_6 à C_{10})pipérazinyle, le 4-hydroxypipérazinyle, le 2,5 diazabicyclo-[2.2.1]hept-2-yle, le 2,5-diaza-5-méthylbicyclo-[2.2.1]hept-2-yle, le 2,3-diaza-3-méthylbicyclo-[2.2.2]oct-2-yle, le 2,5-diaza-5,7-diméthylbicyclo-[2.2.2]oct-2-yle et les diastéréoisomères ou énantiomères desdits groupes [1,n]-diazacycloalkyle et [1,n]-diazacycloalkyle substitué;

un groupe 1-azathiacycloalkyle et un groupe 1-azathiacycloalkyle substitué sélectionnés parmi le thiomorpholinyle, un 2-(alkyle en C_1 à C_3)thiomorpholinyle et un 3-(cycloalkyle en C_3 à C_6) thiomorpholinyle;

un groupe N-azolyle et un groupe N-azolyle sélectionnés parmi le 1-imidazolyle, le 2-(alkyle en C_1 à C_3)-1-imidazolyle, un 3-(alkyle en C_1 à C_3)1-imidazolyle, le 1-pyrrolyle, le 1-pyrazolyle, un 2-(alkyle en C_1 à C_3)-1-pyrrolyle, un 3-(alkyle en C_1 à C_3)-1-pyrazolyle, l'indolyle, le 1-(1,2,3-triazolyl), un 4-(alkyle en C_1 à C_3)-1-(1,2,3-triazolyl), un 5-(alkyle en C_1 à C_3)-1-(1,2,3-triazolyl), le 4-(1,2,4-triazolyl), le 1-tétrazolyle, le 2-tétrazolyle et le benzimidazolyle;

un groupe (hétérocycle)amino sélectionné parmi le 2- ou le 3-furanylamino, le 2- ou le 3-thiénylamino, le 2-, 3- ou 4- pyridylamino, le 2- ou 5-pyridazinylamino, le 2-pyrazinylamino, le 2-(imidazolyl)amino, le (benzimidazolyl)amino et le (benzothiazolyl)amino et un groupe (hétérocycle)amino substitué tel que défini plus haut, la substitution étant sélectionnée parmi un groupe alkyle en C_1 à C_6 linéaire ou ramifié;

un groupe (hétérocycle)méthylamino sélectionné parmi le 2- ou le 3-furylméthylamino, le 2- ou le 3-thiénylméthylamino, le 2-, 3- ou 4- pyridylméthylamino, le 2- ou 5-pyridazinylméthylamino, le 2-pyrazinylméthylamino, le 2-(imidazolyl)méthylamino, le (benzimidazolyl)méthylamino et le (benzothiazolyl) - méthylamino, et un groupe (hétérocycle) méthylamino substitué tel que défini plus haut, la substitution étant sélectionnée parmi un groupe alkyle en C_1 à C_6 linéaire ou ramifié;

un groupe carboxy(alkyle en C_2 à C_4)amino sélectionné parmi l'acide aminoacétique, l'acide α-aminopropionique, l'acide β-aminopropionique, l'acide α-butyrique et l'acide β-aminobutyrique, et les énantiomères dudit groupe carboxy(alkyle en C_2 à C_4)amino;

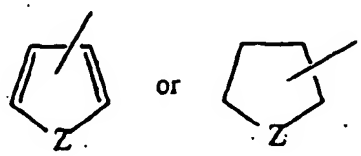
un groupe (alkoxy en C_1 à C_4)carbonylamino, la substitution étant sélectionnée parmi un groupe méthoxycarbonyle, éthoxycarbonyle, allyloxycarbonyle, propoxycarbonyle, isopropoxycarbonyle, 1,1-diméthyléthoxycarbonyle, n-butoxycarbonyle et 2-méthylpropoxycarbonyle;

un groupe (alkoxy en C_1 à C_4)amino, la substitution étant sélectionnée parmi un groupe méthoxy,

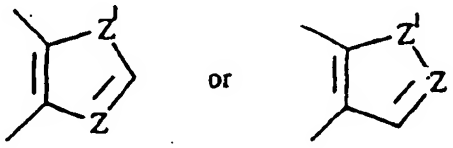
éthoxy, n-propoxy, 1-méthyléthoxy, n-butoxy, 2-méthylpropoxy et 1,1-diméthyléthoxy;
un groupe (cycloalkoxy en C_3 à C_8)amino sélectionné parmi un groupe cyclopropoxy, trans-1,2-diméthylcyclopropoxy, cis-1,2-diméthylcyclopropoxy, cyclobutoxy, cyclopentoxy, cyclohexoxy, cycloheptoxy, cyclooctoxy, bicyclo[2.2.1]hept-2-yloxy, bicyclo[2.2.2]-oct-2-yloxy et les diastéréoisomères et énantiomères dudit groupe (cycloalkoxy en C_3 à C_8) amino;
et
un groupe (aryloxy en C_6 à C_{10}) sélectionné parmi un groupe phénoxyamino, 1-naphtyloxyamino et 2-naphtyloxyamino; un groupe (arylalkoxy en C_7 à C_{11}) amino, la substitution étant sélectionnée parmi un groupe benzyloxy, 2,2-phényléthoxy, 1-phényléthoxy, 2-(naphtyl)méthoxy, 1-(naphtyl) méthoxy et phénylpropoxy;

R^5 et R^6 sont sélectionnés indépendamment parmi:

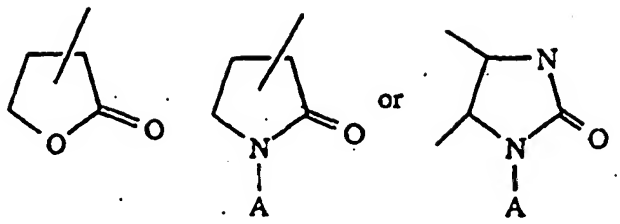
(i) l'hydrogène, avec la condition que R^5 et R^6 ne peuvent représenter tous deux l'hydrogène;
(ii) un groupe alkyle en C_1 à C_3 linéaire ou ramifié sélectionné parmi un groupe méthyle, éthyle, n-propyle ou 1-méthyléthyle;
(iii) un groupe aryle en C_6 à C_{10} sélectionné parmi un groupe phényle, α-napthyle ou β-naphtyle;
(iv) un groupe aralkyle en C_7 à C_9 tel qu'un groupe benzyle, 1-phényléthyle, 2-phényléthyle ou phénylpropyle;
(v) un groupe hétérocyclique sélectionné parmi un cycle aromatique ou saturé à cinq chaînons, avec un hétéroatome N, O, S ou Se auquel un cycle benzo ou pyrido est facultativement fusionné:



Z représente N, O, S ou Se
tel qu'un groupe pyrrolyle, N-méthylindolyle, indolyle, 2-pyrrolidinyle, 3-pyrrolidinyle, 2-pyrrolinyle, tétrahydrofuranyle, furanyle, benzofuranyle, tétrahydrothiényle, thiényle, benzothiényle ou sélénazolyle,
(vi) un cycle aromatique à cinq chaînons avec deux hétéroatomes de N, O, S ou Se auxquels un cycle benzo ou pyrido est facultativement fusionné:



Z ou Z^1 représente N, O, S ou Se
tel qu'un groupe imidazolyle, pyrazolyle, benzimidazolyle, oxazolyle, benzoxazolyle, indazolyle, thiazolyle, benzothiazolyle, 3-alkyl-3H-imidazo[4,5-b]pyridyle ou pyridylimidazolyle,
(vii) un cycle saturé à cinq chaînons avec un ou deux hétéroatomes de N, O, S ou Se et un hétéroatome de O attaché en position adjacente:



(A étant sélectionné parmi un hydrogène, un groupe alkyle en C_1 à C_4 linéaire ou ramifié, un groupe aryle en C_6, un groupe aryle en C_6 substitué (la substitution étant sélectionnée parmi un halogène, un groupe alkoxy en C_1 à C_4, un groupe alkyle trihalogéné en C_1 à C_3, un groupe nitro, amino, cyano, (alkoxy en C_1 à C_4) carbonyle, un groupe (alkyle en C_1 à C_3) amino ou un groupe carboxy; un groupe aralkyle en C_7 à C_9 sélectionné parmi le benzyle, le 1-phényléthyle, le 2-phényléthyle ou le phénylpropyle),

comme le γ-butyrolactam, la γ-butyrolactone, l'imidazolidinone ou la N-aminoimidazolidinone.

(viii) un cycle aromatique à six chaînons avec un à trois hétéroatomes N, par exemple un groupe pyridyle, pyridazinyle, pyrazinyle, triazinyle symétrique, triazinyle asymétrique, pyrimidinyle ou (alkyle en C_1 à C_3)thiopyridazinyle,

(ix) un cycle saturé à six chaînons avec un ou deux hétéroatomes de N, O, S ou Se et un hétéroatome de O attaché en position adjacente, comme le 2,3-dioxo-1-pipérazinyle, le 4-éthyl-2,3-dioxo-1-pipérazinyle, le 4-méthyl-2,3-dioxo-1-pipérazinyle, le 4-cyclopropyl-2-dioxo-1-pipérazinyle, le 2-dioxomorpholinyle, le 2-dioxothiomorpholinyle:

(x) - $(CH_2)_nCOOR^7$, où n représente 0 à 4 et R^7 est sélectionné parmi l'hydrogène; un groupe alkyle en C_1 à C_3 linéaire ou ramifié, sélectionné parmi le méthyle, l'éthyle, le n-propyle et le 1-méthyléthyle; ou

(xi) un groupe aryle en C_6 à C_{10} sélectionné parmi le phényle, l'α-naphtyle et le β-naphtyle:

ou R^5 et R^6 pris ensemble représentent - $(CH_2)_2B(CH_2)_2$-,

B étant sélectionné parmi $(CH_2)_n$ et n représente 0 ou 1, -NH, -N(alkyle en C_1 à C_3 [linéaire ou ramifié]), -N(alkoxy en C_1 à C_4), l'oxygène, le soufre ou des congénères substitués sélectionnés parmi la proline (L ou D) ou le prolinate (L ou D) d'éthyle;

et les sels organiques et minéraux ou complexes métalliques pharmaceutiquement acceptables.

2. Composé selon la revendication 1, dans lequel:

X représente le chlore, le fluor ou un groupe trifluorométhanesulfonyloxy;

R est sélectionné parmi l'hydrogène, le chlore ou -NR^1R^2, R^1 et R^2 représentant indépendamment un groupe méthyle ou éthyle;

R^3 et R^4 représentent indépendamment l'hydrogène, un groupe méthyle ou éthyle, et lorsque R^3 n'est pas identique à R^4, la stéréochimie du carbone asymétrique (c'est-à-dire le carbone portant le substituant W) peut être soit le racémate (DL) soit les énantiomères individuels (L ou D);

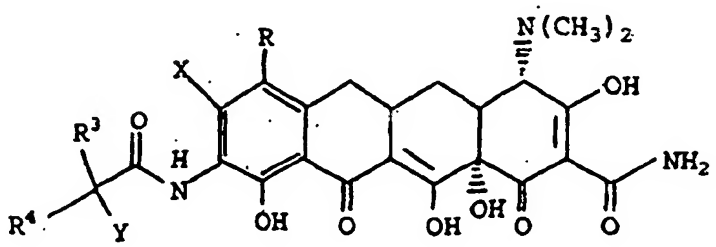
W est sélectionné parmi un groupe amino; un groupe méthylamino éthylamino, n-propylamino, 1-méthyléthylamino, n-butylamino, 1-méthylpropylamino, cyclopropylamino, cyclobutylamino, pyrrolidinyle, pipéridinyle, 4-méthylpipéridinyle, morpholinyle, pipérazinyle, 4-(alkyle en C_1 à C_3)pipérazinyle, 1-imidazolyle, 2-(alkyle en C_1 à C_3)-1-imidazolyle, 3-(alkyle en C_1 à C_3)-1-imidazolyle, 2-, 3- ou 4-pyridylméthylamino, carboxy(alkyle en C_2 à C_4)amino sélectionné parmi l'acide aminoacétique, l'acide α-aminopropionique, l'acide β-aminopropionique, l'acide α-butyrique et l'acide β-aminobutyrique et les énantiomères dudit groupe carboxy(alkyle en C_2 à C_4)amino;

R^5 et R^6 sont sélectionnés indépendamment parmi l'hydrogène, un groupe méthyle, éthyle, n-propyle ou 1-méthyléthyle; avec la condition que R^5 et R^6 ne peuvent tous deux représenter l'hydrogène;

ou R^5 et R^6 pris ensemble représentent - $(CH_2)_2B(CH_2)_2$-, B étant sélectionné parmi $(CH_2)_n$ et n représente 0 ou 1, -NH, -N(alkyle en C_1 à C_3 [linéaire ou ramifié]), -N(alkoxy en C_1 à C_4), l'oxygène, le soufre ou des

congénères substitués sélectionnés parmi la proline (L ou D) ou le prolinate (L ou D) d'éthyle; et les sels organiques et minéraux ou complexes métalliques pharmaceutiquement acceptables.

3. Composé de formule III:



III

dans laquelle

Y est sélectionné parmi le brome, le chlore, le fluor et l'iode; et
R, X, R^3 et R^4 sont comme définis dans la revendication 1.

4. Composé selon la revendication 3, dans lequel:

Y est sélectionné parmi le brome, le chlore, le fluor et l'iode;
X représente ou un groupe trifluorométhanesulfonyloxy, le chlore ou le fluor;
R est sélectionné parmi l'hydrogène, le chlore, l'iode ou $-NR^1R^2$, dans laquelle R^1 et R^2 représentent chacun indépendamment un groupe méthyle ou éthyle;
R^3 est sélectionné parmi l'hydrogène, un groupe méthyle ou éthyle;
R^4 est sélectionné parmi l'hydrogène, un groupe méthyle ou éthyle;

lorsque R^3 n'est pas identique à R^4, la stéréochimie du carbone asymétrique (c'est-à-dire le carbone portant le substituant W) peut être soit le racémate (DL) soit les énantiomères individuels (L ou D); et les sels organiques et minéraux ou complexes métalliques pharmaceutiquement acceptables de ceux-ci.

5. Composé selon les revendications 1 à 3, dans lequel lesdits sels ou complexes métalliques comprennent les sels ou complexes hydrochlorure, hydrobromure, hydroiodure, phosphorique, nitrique, sulfate, acétate, benzoate, citrate, de cystéine ou d'autres acides aminés, de fumarate, glycolate, maléate, succinate, tartrate, alkylsulfonate, arylsulfonate, d'aluminium, de calcium, de fer, de magnésium ou de manganèse.

6. Composé selon la revendication 1, qui est l'un des composés suivants:

disulfate de [4S-(4α,12aα]-8-chloro-4-(diméthylamino)-9-[[(diméthylamino)acétyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide
[Composé de formule I dans laquelle R représente H; X représente Cl; R^3 représente H; R^4 représente H; W représente NMe_2; sel disulphate]
[4S-(4α,12aα]-8-chloro-4-(diméthylamino)-9-[[(diméthylamino)acétyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide
[Composé de formule I dans laquelle R représente H; X représente Cl; R^3 représente H; R^4 représente H]
[4S-(4α,12aα]-8-chloro-4,7-(diméthylamino)-9-[[(diméthylamino)acétyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide
[Composé de formule I dans laquelle R représente NMe_2; X représente Cl; W représente NMe_2; R3 représente H; R^4 représente H]
[4S-(4α,12aα]-9-[[(butylamino)acétyl]amino]-8-chloro-4,7-bis(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide

[Composé de formule I dans laquelle R représente NMe_2; X représente Cl; W représente NHBu; R3 représente H; R^4 représente H]

[7S-(7α,10aα]-N-[9-(aminocarbonyl)-3-chloro-4,7-bis(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-(1-H-pyrrole-1-acétamide

[Composé de formule I dans laquelle R représente NMe_2; X représente Cl; W représente le groupe 1H-pyrrole-1-yle; R^3 représente H; R^4 représente H]

[7S-(7α, 10aα]-N-[9-(aminocarbonyl)-3-chloro-4,7-bis(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-1H-pyrazole-1-acétamide

[Composé de formule I dans laquelle R représente NMe_2; X représente Cl; W représente le groupe 1H-pyrazole-1-yle; R^3 représente H; R^4 représente H]

[4S-(4α,12aα]-8-chloro-4,7-bis(diméthylamino)-9-[[[(1,1-diméthyléthyl) amino] acétyl] amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide

[Composé de formule I dans laquelle R représente NMe_2; X représente Cl; W représente le groupe NHTBu; R^3 représente H; R^4 représente H]

[4S-(4α,12aα]-8-chloro-9-[[(cyclopropylamino)]acétyl]amino]-4,7-bis(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide

[Composé de formule I dans laquelle R représente NMe_2; X représente Cl; W représente le groupe cyclopropylamino; R^3 représente H; R^4 représente H]

[4S-(4α,12aα]-8-chloro-9-[[[(cyclobutyloxy)amino]acétyl]amino]-4,7-bis(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide

[Composé de formule I dans laquelle R représente NMe_2; X représente Cl; W représente le groupe cyclobutyloxyamino; R^3 représente H; R^4 représente H]

[7S-(7α,10aα]-N-[9-(aminocarbonyl)-3-chloro-4,7-bis(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-1-pyrrolidine acétamide

[Composé de formule I dans laquelle R représente NMe_2; X représente Cl; W représente le groupe pyrrolidine-1-yle; R^3 représente H; R^4 représente H]

[4S-(4α,12aα]-8-chloro-4,7-bis(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-9-[[[(propylamino)]acétyl]amino]-2-naphtacène carboxamide

[Composé de formule I dans laquelle R représente NMe_2; X représente Cl; W représente NHPr; R^3 représente H; R^4 représente H]

[4S-(4α,12aα]-8-chloro-4,7-bis(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-9-[[1-oxo-2-(propylamino)]propyl]amino]-2-naphtacène carboxamide

[Composé de formule I dans laquelle R représente NMe_2; X représente Cl; W représente NHPr; R^3 représente H; R^4 représente H]

[4S-(4α,12aα]-4,7-bis(diméthylamino)-9-[[(diméthylamino)]acétyl]amino]-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo--2-naphtacène carboxamide

[Composé de formule I dans laquelle R représente NMe_2; X représente F; W représente NMe_2; R^3 représente H; R^4 représente H]

dihydrochlorure de [4S-(4α,12aα]-9-[[(butylamino)]acétyl]amino]-8-chloro-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxonaphtacène carboxamide

[Composé de formule I dans laquelle R représente H; X représente Cl; W représente NHBu; R^3 représente H; R^4 représente H; dérivé hydrochloré]

dihydrochlorure de [4S-(4α,12aα]-8-chloro-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-9-[[(propylamino)]acétyl]amino]-2-naphtacène carboxamide

[Composé de formule I dans laquelle R représente H; X représente Cl; W représente NHPr; R^3 représente H; R^4 représente H; dérivé hydrochloré]

dihydrochlorure de [4S-(4α,12aα]-8-chloro-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-9-[[(pentylamino)]acétyl]amino]-2-naphtacène carboxamide

[Composé de formule I dans laquelle R représente H; X représente Cl; W représente un groupe phénylamino; R^3 représente H; R^4 représente H; dérivé hydrochloré]

dihydrochlorure de [4S-(4α,12aα]-8-chloro-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-9-[[(méthylamino)]acétyl]amino]-2-naphtacène carboxamide

[Composé de formule I dans laquelle R représente H; X représente Cl; W représente NHMe; R^3 représente H; R^4 représente H; dérivé hydrochloré]

dihydrochlorure de [4S-(4α,12aα]-8-chloro-9-[[(cyclopropylméthylamino)]acétyl]amino]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide

[Composé de formule I dans laquelle R représente H; X représente Cl; W représente un groupe cyclopropylméthylamino; R^3 représente H; R^4 représente H; dérivé hydrochloré]

dihydrochlorure de [7S-(7α,10aα]-N-[9-(aminocarbonyl)-3-chloro-7-(diméthylamino)-5,5a,6,6a,7,10,10a, 12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-1-pyrrolidino acétamide
[Composé de formule I dans laquelle R représente H; X représente Cl; W représente le groupe pyrrolidine-1-yle; R^3 représente H; R^4 représente H; dérivé hydrochloré]

dihydrochlorure de [7S-(7α,10aα]-N-[9-(aminocarbonyl)-3-chloro-7-(diméthylamino)-5,5a,6,6a,7,10,10a, 12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-1-pipéridine acétamide
[Composé de formule I dans laquelle R représente H; X représente Cl; W représente le groupe pipéridine-1-yle; R^3 représente H; R^4 représente H; dérivé hydrochloré]

dihydrochlorure de [7S-(7α,10aα]-N-[9-(aminocarbonyl)-3-chloro-7-(diméthylamino)-5,5a,6,6a,7,10,10a, 12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-5-azabicyclo[2,1,1]hexane-5-acétamide
[Composé de formule I dans laquelle R représente H; X représente Cl; W représente le groupe azabicyclo [2.1.1]hex-5-yle; R^3 représente H; R^4 représente H; dérivé hydrochloré]

dihydrochlorure de [4S-(4α,12aα]-8-chloro-9-[[(cyclobutylamino)]acétyl]amino]-4-(diméthylamino)-1,4,4a, 5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide
[Composé de formule I dans laquelle R représente H; X représente Cl; W représente un groupe cyclobutylamino; R^3 représente H; R^4 représente H; dérivé hydrochloré]

dihydrochlorure de [7S-(7α,10aα]-N-[9-(aminocarbonyl)-3-chloro-7-(diméthylamino)-5,5a,6,6a,7,10,10a, 12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-α-éthyl-1H-imidazole-1-acétamide
[Composé de formule I dans laquelle R représente H; X représente Cl; W représente le groupe 1H-imidazole-1-yle; R^3 représente H; R^4 représente Et; dérivé hydrochloré]

[4S-(4α,12aα]-8-chloro-9-[[2-(diéthylamino)-1-oxopropyl]amino]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide
[Composé de formule I dans laquelle R représente H; X représente Cl; W représente NEt_2; R^3 représente H; R^4 représente H]

[4S-(4α,12aα]-8-chloro-4-(diméthylamino)-9-[[(diméthylamino)(2-fluorophényl)acétyl]amino]-1,4,4a,5,5a, 6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide
[Composé de formule I dans laquelle R représente H; X représente Cl; W représente NMe_2; R^3 représente le groupe 2-fluorophényle; R^4 représente H]

[4S-(4α,12aα]-8-chloro-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-9-[[1-oxo-4-phényl-2-[(phénylméthoxy)-butyl]amino]-2-naphtacène carboxamide
[Composé de formule I dans laquelle R représente H; X représente Cl; W représente $NHCH_2Ph$; R^3 représente le groupe 2-phényléthyle; R^4 représente H]

[4S-(4α,12aα]-4-(diméthylamino)-9-[[(diméthylamino)acétyl]amino]-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide
[Composé de formule I dans laquelle R représente H; X représente F; W représente NMe_2; R^3 représente H; R^4 représente H]

[4S-(4α,12aα]-4-(diméthylamino)-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-9-[[(propylamino)acétyl]amino]-2-naphtacène carboxamide
[Composé de formule I dans laquelle R représente H; X représente F; W représente NHPr; R^3 représente H; R^4 représente H]

[4S-(4α,12aα]-4-(diméthylamino)-9-[[(diméthylamino)acétyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-8-[[(trifluorométhyl)sulfonyl]oxy]-2-naphtacène carboxamide
[Composé de formule I dans laquelle R représente H; X représente $O\text{-}SO_2\text{-}CF_3$; W représente NMe_2; R^3 représente H; R^4 représente H]

7. Composé selon la revendication 3, qui est l'un des composés suivants:

[4S-(4α,12aα]-9-[(chloroacétyl)amino]-8-chloro-4,7-bis(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide
[Composé de formule III dans laquelle R représente NMe_2; X représente Cl; R^3 représente H; R^4 représente H; Y représente Cl]

[4S-(4α,12aα]-9-[(bromoacétyl)amino]-8-chloro-4,7-bis(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide
[Composé de formule III dans laquelle R représente NMe_2; X représente Cl; R^3 représente H; R^4 représente H; Y représente Br]

[4S-(4α,12aα]-9-[(α-bromopropionyl)amino]-8-chloro-4,7-bis(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide
[Composé de formule III dans laquelle R représente NMe_2; X représente Cl; R^3 représente H; R^4 représente

Me; Y représente Br]

[4S-(4α,12aα]-9-[(α-bromophénylacétyl)amino]-8-chloro-4,7-bis(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide

[Composé de formule III dans laquelle R représente NMe_2; X représente Cl; R^3 représente H; R^4 représente Ph; Y représente Br]

[4S-(4α,12aα]-9-[(α-bromo-2,2-diméthylbutyryl)amino]-8-chloro-4,7-bis(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide

[Composé de formule III dans laquelle R représente NMe_2; X représente Cl; R^3 représente le groupe isopropyle; R^4 représente H; Y représente Br]

[4S-(4α,12aα]-9-[(α-bromo-(2,4-difluorophényl)acétyl)amino]-8-chloro-4,7-bis-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide

[Composé de formule III dans laquelle R représente NMe_2; X représente Cl; R^3 représente le groupe 2,4-difluorophényle; R^4 représente H; Y représente Br]

[4S-(4α,12aα]-9-[(bromoacétyl)amino]-4,7-bis(diméthylamino)-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide

[Composé de formule III dans laquelle R représente NMe_2; X représente F; R^3 représente H; R^4 représente H; Y représente Br]

[4S-(4α,12aα]-9-[(bromoacétyl)amino]-4,7-bis-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-8-[(trifluorométhyl)sulfonyl]oxy]-2-naphtacène carboxamide

[Composé de formule III dans laquelle R représente NMe_2; X représente OSO_2CF_3; R^3 représente H; R^4 représente H; Y représente Br; dérivé hydrochloré]

Hydrochlorure du [4S-(4α,12aα]-9-[(chloroacétyl)amino]-8-chloro-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide

[Composé de formule III dans laquelle R représente H; X représente Cl; R^3 représente H; R^4 représente H; Y représente Cl; dérivé hydrochloré]

Hydrobromure du [4S-(4α,12aα]-9-[(bromoacétyl)amino]-8-chloro-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide

[Composé de formule III dans laquelle R représente H; X représente Cl; R^3 représente H; R^4 représente H; Y représente Br; dérivé hydrobromé]

Hydrochlorure du [4S-(4α,12aα]-9-[(2-chloropropionyl)amino]-8-chloro-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide

[Composé de formule III dans laquelle R représente H; X représente Cl; R^3 représente H; R^4 représente Me; Y représente Cl; dérivé hydrochloré]

Hydrochlorure du [4S-(4α,12aα]-9-[(2-chlorobutyryl)amino]-8-chloro-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide

[Composé de formule III dans laquelle R représente H; X représente Cl; R^3 représente H; R^4 représente Et; Y représente Cl; dérivé hydrochloré]

Hydrochlorure du [4S-(4α,12aα]-9-[[(4-hydroxyphényl)-α-chloroacétyl]amino]-8-chloro-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide

[Composé de formule III dans laquelle R représente H; X représente Cl; R^3 représente le groupe 4-hydroxyphényle; R^4 représente H; Y représente Cl; dérivé hydrochloré]

Hydrobromure du [4S-(4α,12aα]-9-[[(2-fluorophényl)-α-bromoacétyl]amino]-8-chloro-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide

[Composé de formule III dans laquelle R représente H; X représente Cl; R^3 représente le groupe 2-fluorophényle; R^4 représente H; Y représente F; dérivé hydrobromé]

Hydrobromure du [4S-(4α,12aα]-9-[(α-bromo-4-phénylbutyryl)amino]-8-chloro-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3 ,10,12, 12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide

[Composé de formule III dans laquelle R représente H; X représente Cl; R^3 représente le groupe 2-phényléthyle; R^4 représente H; Y représente Br; dérivé hydrobromé]

[4S-(4α,12aα]-9-[(bromoacétyl)amino]-4-(diméthylamino)-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide

[Composé de formule III dans laquelle R représente H; X représente F; R^3 représente H; R^4 représente H; Y représente Br]

[4S-(4α,12aα]-9-[(bromoacétyl)amino]-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-8-[[(trifluorométhyl)sulfonyl]oxy]-2-naphtacène carboxamide

[Composé de formule III dans laquelle R représente H; X représente OSO_2CF_3; R^3 représente H; R^4 représente H; Y représente Br].

8. Composé sélectionné parmi:

[4S-(4α,12aα]-8-chloro-4,7-bis(diméthylamino)1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-[[[(3-méthylcyclobutyl)amino]acétyl]amino]-1,11-dioxo-2-naphtacène carboxamide

[Composé de formule I dans laquelle R représente NMe_2; X représente Cl; W représente le groupe 3-méthylcyclobutylamino; R^3 représente H; R^4 représente H]

[7S-(7α,10aα]-N-[9-(aminocarbonyl)-3-chloro-4,7-bis(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,9,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-(3-méthyl-1-pyrrolidine)acétamide

[Composé de formule I dans laquelle R représente NMe_2; X représente Cl; W représente le groupe 3-méthylpyrrolidine-1-yle; R^3 représente H; R^4 représente H]

[7S-(7α,10aα]-N-[9-(aminocarbonyl)-3-chloro-4,7-bis(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-α-cyclobutyl-tétrahydro-2H-1,2-isoxazine-2-acétamide

[Composé de formule I dans laquelle R représente NMe_2; X représente Cl; W représente le groupe tétrahydro-2H-1,2-isoxazine-2-yle; R^3 représente H; R^4 représente H]

[4S-(4α,12aα]-8-chloro-4,7-bis(diméthylamino)-1,4,4a,5,5a 6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-9-[[phényl[(phénylméthyl)amino]acétyl]amino]-2-naphtacène carboxamide

[Composé de formule I dans laquelle R représente NMe_2; X représente Cl; W représente le groupe phényl[(phénylméthyl)amino; R^3 représente H; R^4 représente H]

[7S-(7α,10aα]-N-[9-(aminocarbonyl)-3-chloro-4,7-bis(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-α-cyclopropyl-α-méthyl-1-azétidine acétamide

[Composé de formule I dans laquelle R représente NMe_2; X représente Cl; W représente le groupe azétidine-1-yle; R^4 représente CH_3; R^3 représente un groupe cyclopropyle]

[7S-(7α,10aα]-N-[9-(aminocarbonyl)-3-chloro-4,7-bis(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-α-(1,1-diméthyléthyl)-(3-méthyl-4-morpholine)acétamide

[Composé de formule I dans laquelle R représente NMe_2; X représente Cl; W représente le groupe 3-méthylmorpholine-4-yle; R^3 représente tBu; R^4 représente H]

[4S-(4α,12aα]-8-chloro-9-[[(2,4-difluorophényl)[(2-phényléthyl)amino]acétyl]amino]-4,7-bis(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide

[Composé de formule I dans laquelle R représente NMe_2; X représente Cl; W représente le groupe (2,4-difluorophényl)(2-phényléthyl)amino; R^3 représente H; R^4 représente H]

[7S-(7α,10aα]-N-[9-(aminocarbonyl)-3-chloro-4,7-bis(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-α-(méthoxyamino)-α-méthyl-2-furane acétamide

[Composé de formule I dans laquelle R représente NMe_2; X représente Cl; W représente le groupe NHOMe; R^3 représente le groupe furane-2-yle; R^4 représente un groupe CH_3]

méthylester de l'acide [7S-(7α,10aα]-4-[[9-(aminocarbonyl)-3-chloro-4,7-bis(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-amino-3-[(1,1-diméthyléthyl)amino]-4-oxobutanoïque

[Composé de formule I dans laquelle R représente NMe_2; X représente Cl; W représente le groupe NHTBu; R^3 représente le groupe CH_2COOMe; R^4 représente H]

méthylester de l'acide [7S-(7α,10aα]-4-[[9-(aminocarbonyl)-3-chloro-4,7-bis(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]amino]-3-(diméthylamino)-4-oxobutanoïque

[Composé de formule I dans laquelle R représente NMe_2; X représente Cl; W représente NMe_2; R^3 représente CH_2COOMe; R^4 représente H]

méthylester de l'acide [7S-(7α,10aα]-γ-[[[9-(aminocarbonyl)-3-chloro-4,7-bis(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]amino]carbonyl]-1-pyrrolidine butanoïque

[Composé de formule I dans laquelle R représente NMe_2; X représente Cl; W représente le groupe pyrrolidin-1-yle; R^3 représente CH_2CH_2COOMe; R^4 représente H]

méthylester de la [7S-(7α,10aα]-1-[2-[[9-(aminocarbonyl)-3-chloro-7-(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]amino]-1-méthyl-2-oxoéthyl]proline

[Composé de formule I dans laquelle R représente H; X représente Cl; W représente le groupe 2-méthoxycarbonyl-pyrrolidin-1-yle ; R^3 représente CH_3; R^4 représente H]

[7S-(7α,10aα]-N-[9-(aminocarbonyl)-3-chloro-7-(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-α-(4-hydroxyphényl)-6-méthyl-2,6-diazabicyclo-[2.1.1.]heptan-2-acétamide

[Composé de formule I dans laquelle R représente H; X représente Cl; W représente le groupe 6-méthyl-2,6-diazabicyclo-[2.1.1.]heptan-2-yle ; R^3 représente l'hydroxyphényle; R^4 représente H]

[4S-(4α,12aα]-8-chloro-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-[[(1-(4-méthoxy-1-pipérazinyl)-4-pentènoyl]amino]-1,11-dioxo-2-naphtacène carboxamide
[Composé de formule I dans laquelle R représente H; X représente Cl; W représente le groupe 4-méthoxypipérazin-1-yle; R^3 représente $CH_2CH_2CH=CH_2$; R^4 représente H]

[7S-(7α,10aα]-N-[9-(aminocarbonyl)-3-chloro-7-(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-α-4-pyridyl-5-azabicyclo[2.1.1.]hexan-5-acétamide
[Composé de formule I dans laquelle R représente H; X représente Cl; W représente l'azabicyclo-[2.1.1.]hex-1-yle ; R^3 représente le groupe 4-pyridyle; R^4 représente H]

9. Composé sélectionné parmi

[4S-(4α,12aα]-9-[(α-bromocyclobutylacétyl)amino]-8-chloro-4,7-bis-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide
[Composé de formule III dans laquelle R représente NMe_2; X représente Cl; R^4 représente H; R^3 représente le groupe cyclobutyle; Y représente Br]

[4S-(4α,12aα]-9-[(α-bromo-α-cyclopropylpropionyl)amino]-8-chloro-4,7-bis-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide
[Composé de formule III dans laquelle R représente NMe_2; X représente Cl; R^3 représente le groupe cyclopropyle; R^4 représente Me; Y représente Br]

[4S-(4α,12aα]-9-[(α-bromo-α-(2-furyl)propionyl)amino]-8-chloro-4,7-bis(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide
[Composé de formule III dans laquelle R représente NMe_2; X représente Cl; R^3 représente le groupe furanylméthyle; R^4 représente H; Y représente Br]

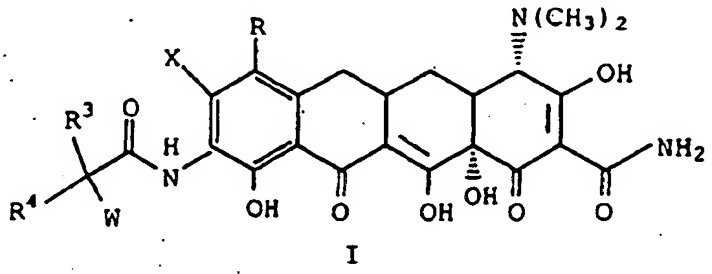
[4S-(4α,12aα]-9-[(α-bromo-α-(3-méthoxy-carbonylpropionyl))amino]-8-chloro-4,7-bis-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide
[Composé de formule III dans laquelle R représente NMe_2; X représente Cl; R^3 représente le groupe méthoxycarbonylméthyle; R^4 représente H; Y représente Br]

[4S-(4α,12aα]-9-[(α-bromo-α-(4-méthoxycarbonylbutyryl))amino]-8-chloro-4,7-bis-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide
[Composé de formule III dans laquelle R représente NMe_2; X représente Cl; R^3 représente le groupe méthoxycarbonyléthyle; R^4 représente H; Y représente Br]

hydrobromure du [4S-(4α,12aα]-9-[(2-bromo-4-penténoyl)amino]-8-chloro-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide
[Composé de formule III dans laquelle R représente H; X représente Cl; R^3 représente-$CH_2CH{-}CH_2$; R^4 représente H; Y représente F: dérivé hydrobromé]

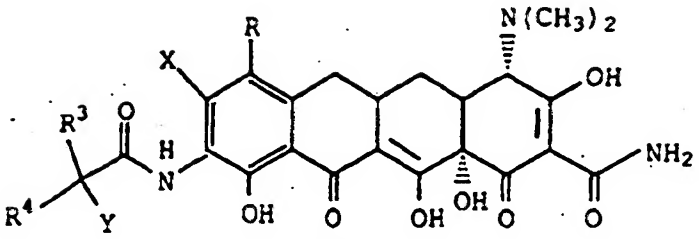
hydrobromure du [4S-(4α,12aα]-9-[((4-pyridyl) - α-bromoacétyl)amino]-8-chloro-4-(diméthylamino)-1,4,4a,5,5a, 6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacène carboxamide
[Composé de formule III dans laquelle R représente H; X représente Cl; R^3 représente le groupe 4-pyridyle; R^4 représente H; Y représente Br; dérivé hydrobromé]

10. Procédé de production d'un composé de formule (I) ou de ses sels organiques ou minéraux ou complexes métalliques de formule:



I

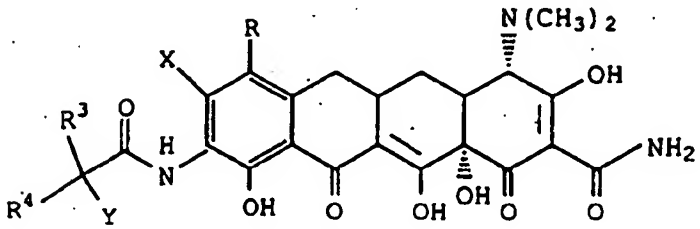
selon la revendication 1, qui comprend la mise en réaction d'une 9-[(haloacyl)amido]-7-(substitution)-8-(substitution)-6-déméthyl-6-désoxytétracycline ou de son sel organique ou minéral ou complexe métallique de formule



III

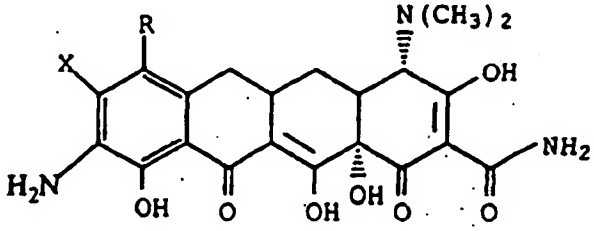
selon la revendication 3, avec un nucléophile de formule WH dans laquelle W est comme défini à la revendication 1, dans un solvant protonique polaire ou aprotonique polaire et sous une atmosphère inerte.

11. Procédé de production d'un composé ou de son sel organique ou minéral ou son complexe métallique de formule

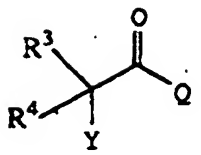


III

selon la revendication 3, qui comprend la mise en réaction d'une 9-amino-7-(substitution)-8-(substitution)-6-déméthyl-6-désoxytétracycline ou son sel inorganique ou minéral ou complexe métallique de formule:

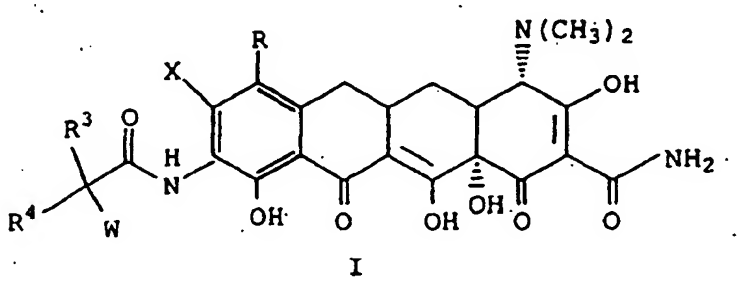


avec un halogénure d'haloacyle linéaire ou ramifié de formule:



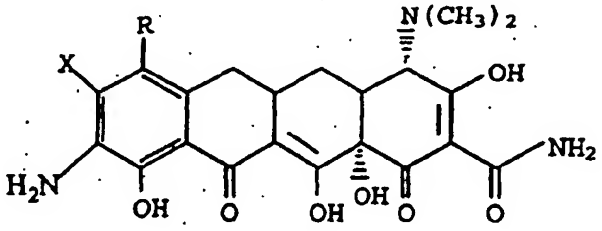
dans laquelle Y, R^3 et R^4 sont comme définis à la revendication 1 et Q est un halogène sélectionné parmi le brome, le chlore, l'iode et le fluor, dans un solvant inerte, dans un solvant protonique polaire et en présence d'une base.

12. Procédé de production d'un composé ou de son sel organique ou minéral ou de son complexe métallique de formule:

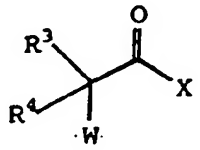


I

selon la revendication 1, qui comprend la mise en réaction d'une 9-amino-7-(substitution)-8-(substitution)-6-déméthyl-6-désoxytétracycline ou son sel organique ou minéral ou son complexe métallique de formule:

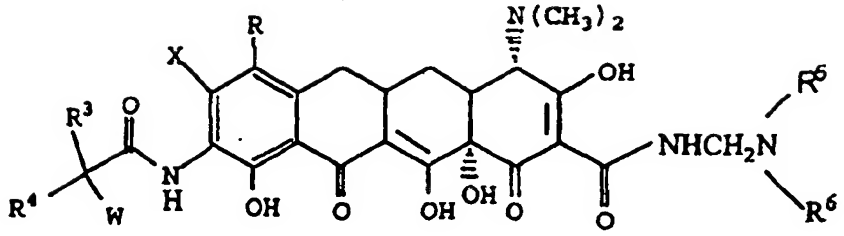


avec un chlorure d'acide linéaire ou ramifié de formule:



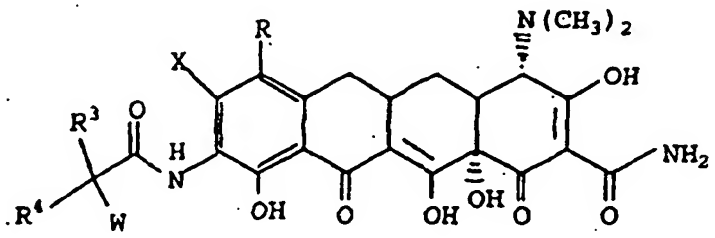
dans laquelle R^3, R^4 et W sont comme définis à la revendication 1 et X représente un halogène sélectionné parmi le brome, le chlore, l'iode et le fluor dans un absorbant acide approprié et un solvant approprié.

13. Procédé de production d'un composé de formule:



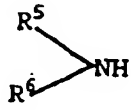
II

selon la revendication 1, qui comprend la mise en réaction d'un 9-[(glycyl substitué)amido]-7-(substitution)-8-(substitution)-6-déméthyl-6-dioxytétracycline de formule:



I

selon la revendication 1 avec une amine primaire de formule R^5NH_2 ou une amine secondaire de formule:



en présence d'un formaldéhyde.

14. Utilisation d'un composé selon la revendication 1 pour la préparation d'un médicament pour la prévention, le traitement ou le contrôle d'infections bactériennes chez des animaux à sang chaud.

15. Composition pharmaceutique comprenant une quantité pharmacologiquement active d'un composé selon la revendication 1 en association avec un support pharmaceutiquement acceptable.

16. Composition vétérinaire qui comprend une quantité pharmacologiquement active d'un composé selon la revendication 1 en association avec un support pharmaceutiquement acceptable.

17. Utilisation d'un composé selon la revendication 1 pour la préparation d'un médicament pour la prévention, le traitement ou le contrôle d'infections bactériennes provoquées chez des animaux à sang chaud par des bactéries présentant des déterminants résistant au TetM et au TetK.